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CARBONIC ANHYDRASE INHIBITION. VIII. LACK OF RENAL RESPONSE TO ACETAZOLAMIDE AND TO MERALLURIDE IN A DOG WITH CHRONIC NEPHRITIS

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THE failure of mercurials[1,2] or a carbonic anhydrase inhibitor, acetazolamide, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide,[2,3,4] to cause diuresis in the presence of renal disease is well known. In the case of mercurials, it has been suggested that decrease in filtration rate and "glomerulotubular imbalance" leads to virtually complete reabsorption of sodium, even in the presence of the diuretic.[1] In the case of acetazolamide, it has been suggested that carbonic anhydrase is absent from the diseased kidney.[4]

The spontaneous occurrence of severe nephritis in a trained female beagle in our colony gave the opportunity to study the renal response to acetazolamide and to meralluride in this disease under carefully controlled conditions. Observations were of particular interest, since the dog had received acetazolamide on several occasions 2 years previously, before renal function had deteriorated. In the diseased state, there was no response to acetazolamide, and there were negligible quantities of urinary ammonia, despite extremely acid urine. Because of these findings, carbonic anhydrase and glutaminase were measured in the kidneys of this dog, following their removal immediately after death.

METHODS AND MATERIALS

General methods have been described.[5] Additions pertinent to the present paper follow.

Carbonic anhydrase was determined by an adaption of the changing pH method of Philpot.[6] Glutaminase was determined by the method of Archibald.[7] Both *p*-aminohippuric acid (PAH) and creatinine were determined on aliquots of filtrates following protein precipitation with cadmium sulfate in sulfuric acid solution.[8]

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Intravenous acetazolamide was given as a 5 per cent solution of the sodium salt, made by adding 1.6 moles NaOH per mole of drug. Meralluride sodium solution was given intramuscularly; each milliliter contains 39 mg. Hg (U.S.P. XV).

EXPERIMENTAL

Development of Nephritis in Dog M 52.—The subject was a female beagle (M 52) born in this colony on Jan. 2, 1946. Her history was unremarkable until the time that proteinuria was noticed in November, 1952. Between 1947 and 1951, she had three normal litters, came into heat usually twice a year, and seemed entirely well. During this time she received distemper vaccine, vitamins, tetrachlorethylene, and chlortetracycline. She also received two doses of one experimental drug (Polymyxin) and one dose of another (CL 6434, 1-anilino-6,7-dimethoxyisoquinoline hydrochloride dihydrate). She was not used in any chronic toxicity tests.

In February and March, 1952, M 52 was used in several acute studies on the pharmacology of acetazolamide.[9] Following the administration of drug, there was the usual alkalinization of urine (to pH 7.9), fourfold increase in urine flow, and approximately 40 per cent of the acetazolamide was recovered in the urine in 3 hours. Creatinine clearance was 30-50 ml. per minute. In one test (Fig. 3,*C*[9]) there was a delay in onset of the renal effect: this was then regarded as a normal variation, but in the light of further experience, this now appears abnormal. In general, however, these tests in M 52, during 1952, showed responses to acetazolamide and renal function like those of other dogs in the colony.

On Sept. 30, 1952, M 52 was found to have normal creatinine (40 ml. per minute) and PAH (155 ml. per minute) clearance. Urinary protein was 4+. Subsequent tests in October and November, 1952, showed continued proteinuria from 1+ to 4+, some white cells, red cells, and epithelial casts in the urine. On November 4, she responded normally to acetazolamide at 33 mg. per kilogram by mouth with augmented urinary excretion of Na^+, K^+, HCO_3^- and water. Weight was then 15.1 Kg.

Because of the persistent proteinuria, the dog was not used for 2 years, during which time she continued in good health. Weight fluctuated between 15 to 17 Kg. On Oct. 19, 1954, she was given a single low dose of a carbonic anhydrase inhibitor related to acetazolamide, which had previously been shown active in vivo. However, there was no response in M 52. Three days later a similar study was done with acetazolamide (5 mg. per kilogram oral); again there was no response. At that time the dog appeared well but had lost weight (weight = 13 Kg.). Urinary findings were: specific gravity 1.007 (concentration test), protein 3+, WBC 50-100/HPF, RBC 50-75/HPF, and hyaline casts. On October 27 and 29, a complete blood electrolyte study was done; clearance studies were also carried out in this period. These data are given in Table I. It was evident that M 52 had severe nephritis of unknown origin. The following section gives data on the administration of intravenous acetazolamide and intramuscular meralluride to this animal.

TABLE I. CHEMICAL FINDINGS IN DOG M 52

	PLASMA							BLOOD MG./100 C.C.		CLEARANCE (RANGE OF FOUR PERIODS) ML./MIN.	
		HCO_3^-	pCO_2	mM/LITER							
M 52	pH	mM/L.	MM./HG	CL^-	(PO_4)	Na^+	K^+	NPN	UREA N	CREATININE	PAH
Oct. 27, 1954	7.30	15.3	32	98	3.6	150	3.7	179	160		
Oct. 28, 1954										2–3	8–12
Oct. 29, 1954	7.27	17.6	39	90	4.4	152	3.3	156	130		

Normal values and ranges are available from previous studies in this laboratory.[5,9]

Clearances were done in 20-minute periods, beginning 1 hour after subcutaneous injection of 60 mg./Kg. PAH and 200 mg./Kg. creatinine.

The following are regarded as abnormal: HCO_3^- is 3-5 mM/L. low; PO_4 is 2-3 mM/L. high; NPN and Urea N are very high; pH is slightly low and Na^+ is slightly high. Clearances are about 1/15 to 1/20 of normal. See text for previous clearances in M 52.

Renal Effect of Acetazolamide and Meralluride in M 52.—Table II shows that acetazolamide and meralluride had no effect on urinary composition of M 52 during the same 3-day period covered in Table I. The urine was dilute, with flow somewhat above normal. Excretion rates and concentrations of electrolytes were very low, compared with well dogs in the colony.[5] NH_4^+ output was low in relation to the titrable acid. Urinary pH was very low, but there was less titrable acid for this pH range than in the normal. It appeared probable that acidification mechanisms would not alone be adequate to defend the body against loss of Na^+; however, the grossly lowered filtration rate would mitigate against the general depletion of electrolytes.

The doses of acetazolamide[5] and meralluride[10] used in the experiments of Table II have been shown to give good responses in the normal dog. Lack of response to acetazolamide in M 52 prompted determination of renal carbonic anhydrase in this dog. Mercury-sensitive enzymes which control renal transport are not known. Renal glutaminase was also measured, in view of the low urinary ammonia. (These determinations are discussed in the next section.)

Renal Carbonic Anhydrase and Glutaminase in M 52.—M 52 was sacrificed with intravenous pentobarbital on Oct. 29, 1954. Just prior to the anesthetic, 5 ml. of Heparin was injected intravenously. The abdomen was opened and the aorta clamped above and below the renal arteries.

Carbonic Anhydrase Assay.—The left renal artery was perfused in situ with saline, until the kidney appeared free of blood. It was then removed, and cortex and medulla separated. These portions, and the remainder, were each ground with water to make a 1:20 suspension. The total time elapsed from injection of pentobarbital to analyses of enzyme was 66 minutes. The entire kidney, which weighed 33 grams after perfusion, contained 2,160 enzyme units, or 66

units per gram.* A control dog (M 97) with no evidence of renal disease was subjected to the same procedure. The kidney weighed 29 grams and contained 3,480 enzyme units, or 120 units per gram. Although the kidney of M 52 had less carbonic anhydrase than the control, it does not seem likely that a difference of this magnitude could account for the total lack of response to acetazolamide. A moderate degree of variability was encountered by Davenport and Wilhelmi[12] in their study of kidney carbonic anhydrase in normal dogs.

TABLE II. FAILURE OF RENAL RESPONSE TO ACETAZOLAMIDE AND TO MERALLURIDE IN A DOG WITH CHRONIC NEPHRITIS

URINE									ACETAZOLAMIDE	
TIME (MINUTES)	FLOW ML./MIN.	pH	MICROEQUIVALENTS/MINUTE						MG.	CUM. % DOSE
			HCO_3^-	CL^-	T. A.	NH_4^+	Na^+	K^+		
Oct. 27, 1954										
−60 to −30	.23	5.0	<1	1	4	<1	2	5		
−30 to 0	.41	5.0	<1	3	6	2	4	8		
0	Acetazolamide, 5 mg./Kg. intravenously									
0 to 60	.27	5.7	<1	2	3	<1	2	10	1	1.7
60 to 120	.35	5.4	<1	2	6	2	2	10	1	3.3
120 to 180	.34	4.9	<1	2	5	1	2	8	0.8	4.6
Oct. 28, 1954										
−40 to 0	.27	4.8	<1	1			2	5		
0	Meralluride, 0.8 ml./Kg. intramuscularly									
0 to 120	.38	4.9	<1	4			4	4		

Dog blood contains about three to four times the concentration of carbonic anhydrase as does kidney, as observed previously[12] and confirmed here. In the method used, the kidneys were essentially free of blood; certainly much less than 2 per cent of their weight was red cells.[12] Enzyme measured, therefore, can be regarded as renal.

Glutaminase Assay.—The right kidney was removed. One portion was taken for pathologic examination and one for glutaminase determinations,[7] which were kindly carried out by Mr. D. S. Davies. In the kidney of M 52, there were 16 units per gram. In 10 control dogs, the range was 10 to 30 units per gram.

Pathologic Findings.—Autopsy was performed by Dr. Edmund Mayer of the Pathology Group of these Laboratories to whom we are indebted for the following data and interpretation.

Data: The kidneys were of similar size and showed a hard consistency and granular surface. The right one was used for the morphologic studies. The following abnormalities were seen: interstitial lymphocytic accumulations, connective tissue scars, renal corpuscles with greatly dilated spaces of Bowman's

*The cortex contained 95 and the medulla 30 units per gram.

capsule, fibrosis of renal corpuscles of different stages, and an alternation of compressed and dilated tubules with a large number of protein casts. Every renal corpuscle shows at least a pronounced thickening of the wall of Bowman's capsule. A rough estimate based on the count of 360 corpuscles shows that approximately 24 per cent could possibly have functioned normally, while 42 per cent were completely fibrosed and 34 per cent partially so. However, many of the "good" corpuscles seemed to be connected to blocked tubules; the number of nephrons which possibly could have functioned well appeared very small.

Most arteries and arterioles in the kidney appeared normal.

Other organs appeared normal, except for large amounts of iron-positive pigment in liver and spleen.

Interpretation: The kidney described here could be either an advanced phase of glomerulonephritis of the type which is common in humans, but rare in dogs, or it could be the advanced phase of interstitial nephritis of the type which is very common in dogs. The diagnosis of canine interstitial nephritis is more likely because of the following morphologic reasons: absence of epithelial crescents in the renal corpuscles, negligible amount of renal arteriosclerosis, and presence of lymphocytic accumulations in the interstitium. The functional findings were compatible with either diagnosis; the blood pressure is not elevated in interstitial canine nephritis, and need not be elevated in the latent phase of chronic glomerulonephritis of the human type. The anemia observed could be a sequela of either type of renal disease.

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DISCUSSION

This study was of particular interest because the animal had been given acetazolamide both before and after the stage of late nephritis, and because this nephritis had the following functional findings in common with the human disease: azotemia, moderate plasma acidosis, high plasma phosphorous, dilute urine, proteinuria, acid urine with relatively low titratable acid and very low NH_4^+, anemia, low creatinine and PAH clearance, and casts and RBC and WBC in urine.

The present findings agree with those of Weston and associates,[1] which implicate low filtration rate in renal disease as a factor in nonresponse to mercurial diuretics. Our data extend this to the case of the carbonic anhydrase inhibitor, acetazolamide.

Low filtration rate is suggested as the reason for nonresponse on the basis of these observations. The plasma electrolyte pattern did not show any marked abnormality. The mild metabolic acidosis would be expected to augment the response to mercury, and by comparison to our earlier data, was not severe enough to abolish the acetazolamide effect.[13] There was no evidence that marked depletion of any ion was taking place. With particular respect to nonresponse to acetazolamide, it was conceivable that carbonic anhydrase was absent from the diseased kidney.[4] Such was not the case. Although excretion of acetazolamide was low as a result of impaired renal function (about 1 mg. per hour), this rate is associated with alkalinization of urine in the normal dog.[14] Thus, it may be

assumed that enzyme was present and that the inhibitor had access to the enzyme. In the normal kidney, mercurials and acetazolamide can at most divert but 40 per cent of filtered Cl^- and HCO_3^-, respectively, into the urine. The remainder (over 60 per cent) appears to be reabsorbed by process(es) which cannot be influenced by these drugs. There is some evidence that the drug-dependent processes disappear first, when the kidney is subject to certain abnormal situations.* Thus, in metabolic acidosis, response to acetazolamide is abolished, and complete reabsorption of HCO_3^- continues, presumably without carbonic anhydrase as a rate-controlling factor.[13] Similarly, in the Na^+ and Cl^- depleted animal, meralluride has no effect.[11]

We may suppose that the drug-dependent processes are concerned with the more readily affected fraction of filtered loads of the ions under consideration. This correspondence is not necessarily an exact one; in certain circumstances plasma HCO_3^- may be considerably reduced (to about 60 per cent of normal) without altering the renal response to acetazolamide.[5] But consequent to the long-term and severe nephritis in M 52, filtration had been reduced to about 6 per cent of normal; the very small amounts of filtered HCO_3^- and Cl^- appear to be reabsorbed by processes insusceptible to the diuretics under study.

The finding of glutaminase in a kidney unable to excrete NH_4^+ in acid urine is of interest and suggests the investigation of steps other than the enzymatic splitting of glutamine in this common defect of late nephritis.

SUMMARY

A case of advanced nephritis in a 9-year-old female beagle has been studied, with particular reference to response to acetazolamide and meralluride. Both drugs failed to produce their typical renal effects. Carbonic anhydrase and glutaminase were found in the kidneys. Glomerular filtration rate was 6 per cent of normal. Lack of renal response to both acetazolamide and meralluride is attributed to the very low filtration of HCO_3^- and Cl^-; it is probable that the processes for reabsorption of such small quantities of these ions cannot be affected by ordinary diuretic drugs.

We wish to thank Mrs. Lillian A. Wozniak, Mrs. Barbara W. Koenitzer, and Miss Clara Pellici for their careful performance of these experiments.

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*Conforming to the suggestion that the drug-independent processes are more basic to the organism, they are also probably more primitive, since the elasmobranch kidney responds neither to mercury[15] nor to acetazolamide.[16]

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THE CIRCULATORY RESPONSE TO SMOKING

The Variation in Ballistocardiographic Smoking Tests in Healthy Young Men

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DURING the course of a project to discover what characteristics in the individual are of value in recognizing susceptibility to hypertension and coronary heart disease, a study of the circulatory response to smoking in healthy young adults was reported, in 1956, by Thomas, Bateman, and Lindberg.[1] Various patterns of response were described, and the mean patterns of subjects grouped on the basis of sex, body weight, smoking habits, or family history were compared. The most striking differences found were those associated with family history. On the average, subjects with a history of parental hypertension appeared much more reactive than did those with normal parents, while subjects with a history of parental coronary disease showed less response of blood pressure, heart rate, and cardiac output than either of the other two groups. Since both hypertension and coronary disease are thought to depend in part on genetic factors, these varying patterns of circulatory response to smoking may stem from inherited constitutional differences. If so, they would provide early indications of liability to cardiovascular disease in later life.

It is clear that differences in the pattern of response to smoking arise from two main sources of variation—true "constitutional" differences between individuals, and variations in physiologic responsiveness of the individual from time to time. It is also clear that however valuable this test may be in distinguishing between different groups, it will be of little value in individual prognosis unless the former source of variation is much more important than the latter. Accordingly, studies have been undertaken (1) to measure the reproducibility of results under standard conditions, and (2) to ascertain what factors influence the results and therefore should be standardized if the maximum amount of information is to be derived from smoking tests.

This study was supported in part by the Tobacco Industry Research Committee, in part by Research Grant H-1891, National Heart Institute and in part by Research Contract V1001 M-2768, Veterans Administration.

MATERIALS AND METHODS OF PROCEDURE

All the subjects were Johns Hopkins medical students in good health and free from clinical, electrocardiographic, and ballistocardiographic evidences of hypertension or coronary heart disease. They were of comparable age and were all male smokers. The same Technitrol table ballistocardiograph was used throughout. The details of the method used in performing the smoking test and in analyzing the ballistocardiographic measurements were as previously described.[1]

Three series of smoking tests provided material for this study.

Series O.—Number of subjects: 69. Mean age in years at last birthday: 24.86 ±0.27.

Of the 113 individuals whose single smoking tests have already been reported, 69 were male smokers.[1] The data for these subjects are here freshly analyzed after excluding the female subjects and the nonsmokers for the sake of homogeneity. These tests were performed at various times of day from 9:30 A.M. to 5:20 P.M. Two-thirds were performed between 2:30 P.M. and 5:00 P.M. With rare exceptions, at least 1 hour had elapsed since the last meal.

Series F.—Number of subjects: 32. Mean age in years at last birthday: (1) for "I" tests 23.16 ±0.27, (2) for "II" tests 23.31 ±0.26.

Four smoking tests were performed on each of the 32 male smokers in the class of 1958, between October, 1955, and June, 1956. The four tests on each individual consisted of two tests on each of two days (I and II), one before breakfast (A) and one before lunch (B). The first pair of tests (IA and IB) was carried out on a day in the fall of 1955, the second pair (IIA and IIB) on a day during that winter or in the spring of 1956. All of the 128 tests were performed by one of three assistants; almost always, each pair of tests was carried out by the same assistant.* The subject came to the laboratory at 8:00 A.M. without smoking, without breakfast, and without drinking coffee. He was weighed and measured, after which he lay quietly on the ballistocardiograph. The A test was then done in accordance with the method previously described except that the subject smoked one cigarette instead of two, and no electrocardiographic tracings were recorded.[1] After the A test he breakfasted, smoked if he pleased, and attended morning classes as usual, returning to the laboratory before lunch for the second (B) test of the day. He was not, however, allowed to smoke between 12:00 noon and his B test which was performed at 1:00 P.M.

The two tests on the same day, then, differed in the following respects: (1) for the A test the subject had been fasting overnight, for the B test for the 4 hours since breakfast only; (2) the subject was allowed to smoke up to 1 hour before his B test, but not for 8 hours before his A test; and (3) he had been inactive for most of the previous 8 hours before the A test, whereas before his B test, he had been occupied with the usual second year academic activities.

*We should like to acknowledge the assistance of Dr. Amarili Kassam, part-time fellow, who performed many of the smoking tests.

The tests on the second day (IIA and IIB) were carried out as nearly as possible in the same manner as those on the first day.

Series E.—Number of subjects: 6. Mean age in years at last birthday: (1) at first test 23.33 ±0.42, (2) at last test 23.67 ±0.33.

Over a period of 9 weeks in the summer of 1956, each of 6 male smokers underwent a series of eight smoking tests performed as far as possible under circumstances identical for each individual and conducted by the same observer (EAM). On the 8 test days, each subject followed a uniform pattern of activity, took a uniform amount of exercise, smoked the same number of cigarettes at the same time of day, and ate the same types of meals at the same times of day. The tests were performed at a time of day constant within 5 minutes either way for each individual, and all between 2:00 and 5:00 P.M. (resembling the majority of studies in series O). Since the period of time over which the observations were made was brief, weather conditions were fairly constant. It will thus be seen that while there were differences *between* individuals, for any *one* individual, the circumstances were as nearly as possible absolutely uniform. The ballistocardiographic measurements were all made by the same two technical assistants working together.

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Consideration of these three series shows a varying degree of standardization: (1) series O: in this series all subjects were healthy young male smokers; (2) series F: all the subjects were healthy young male smokers and the tests were performed at two standard times of day under two standard conditions of smoking and eating; (3) series E: all the subjects were healthy young male smokers, whose eating, smoking, and exercise habits were, within the individual, uniform and the observer and the time at which the test was performed unvaried. The weather conditions were also fairly constant.

Most of the statistical techniques used in these analyses are described in Snedecor's textbook.[2] The use of "t" tests has been restricted to groups of figures found to have a normal distribution. The meaning of asterisks to denote levels of significance is defined in the footnotes.

RESULTS

The Interindividual Range of Circulatory Response to Smoking: the Series of Single Smoking Tests in 69 Subjects (Series O).—The means and variances for the results obtained in the 69 single smoking tests (Series O) are shown in Table I. Despite the greater homogeneity of the present group as the result of discarding the nonsmokers and the women, the findings are essentially the same as those for the 113 individuals set forth in the first table of the preceding paper.[1] The main importance of the new calculations here given in Table I is for the purposes of comparison with groups E and F (see below).

Comparison of Variation Within the Individual and Between Individuals Under Different Standardized Fasting Conditions: the Series of Two Tests Before Breakfast and Before Lunch on Each of 32 Subjects (Series F).—The results of

TABLE I. ANALYSIS OF RESULTS OBTAINED IN 69 SINGLE SMOKING TESTS ON MALE SMOKERS

MEASUREMENT	MEAN	$(S.D.)^2$	S.D.	S.E.M.
Systolic pressure				
Control	114.2	92.66	9.63	1.16
Change	2.61***	36.48	6.04	0.73
Final	116.8	100.84	10.04	1.21
Diastolic pressure				
Control	71.6	49.44	7.03	0.85
Change	4.93***	24.19	4.92	0.59
Final	76.6	59.28	7.70	0.93
Pulse pressure				
Control	42.6	87.37	9.35	1.13
Change	−2.32**	45.04	6.71	0.81
Final	40.2	102.72	10.14	1.22
Heart rate				
Control	70.8	122.03	11.05	1.33
Change	7.50***	48.01	6.93	0.83
Final	78.3	131.18	11.45	1.38
Stroke volume				
Control	109.7	250.07	15.81	1.90
Change	−3.84***	43.91	6.63	0.80
Final	105.9	297.48	17.25	2.08
Cardiac output				
Control	7.69	1.585	1.259	0.152
Change	0.473***	0.559	0.748	0.090
Final	8.16	2.081	1.443	0.174

These probability values are based on "t" tests for significance of change on smoking as compared with the variation in the change on smoking.

Probabilities are indicated by asterisks as follows:

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

Abbreviations: S.D. = standard deviation; S.E.M. = standard error of the mean.

Blood pressure is recorded throughout in mm. Hg, heart rate in beats per minute, stroke volume in milliliters, and cardiac output in liters per minute.

this series of 128 smoking tests on 32 subjects are summarized in Table II.* Smoking one cigarette produces, in each instance, a highly significant mean rise in systolic and diastolic pressure, heart rate, and cardiac output and a significant mean fall in stroke volume. In the main, the systolic and diastolic pressures rise in parallel so that the mean pulse pressure is little affected. In Test IIB, however, the pulse pressure falls by an amount which is just significant. This pattern is substantially the same as that in the O series; the higher probability of significance for the change in the pulse pressure in the latter is in part a reflection of the larger number of observations.

*Because one of the series of ballistocardiograms was technically unsatisfactory in each of two subjects, all the calculations derived therefrom (heart rate, stroke volume, and cardiac output) were discarded. Thus there are data on blood pressure in 32 subjects and on the cardiac measurements in 30.

TABLE II. THE EFFECTS OF SMOKING UNDER DIFFERENT CONDITIONS IN THE FASTING STATE: FOUR TESTS ON EACH OF 32 MALE SMOKERS (SERIES F)

OBSERVATION	N	IA. THE FIRST TEST BEFORE BREAKFAST					IIA. THE SECOND TEST BEFORE BREAKFAST				
		CONTROL MEAN	CHANGE AFTER ONE CIGARETTE				CONTROL MEAN	CHANGE AFTER ONE CIGARETTE			
			MEAN	S.D.	S.E.M.	t		MEAN	S.D.	S.E.M.	t
Systolic pressure	32	113.2	+5.4	6.56	1.16	4.63***	112.9	+6.5	6.49	1.15	5.70***
Diastolic pressure	32	66.3	+5.1	5.49	0.97	5.21***	67.0	+6.0	5.63	1.00	5.90***
Pulse pressure	32	46.9	+0.3	4.54	0.80	0.39	45.9	+0.7	4.27	0.75	0.87
Heart rate	30	60.8	+13.3	10.3	1.88	7.09***	60.0	+13.3	12.1	2.20	6.06***
Stroke volume	30	109.4	−6.2	10.1	1.84	3.35**	110.6	−5.5	9.46	1.73	3.18**
Cardiac output	30	6.57	+1.03	0.99	0.18	5.72***	6.60	+1.10	1.26	0.23	4.76***
		IB. THE FIRST TEST BEFORE LUNCH					IIB. THE SECOND TEST BEFORE LUNCH				
Systolic pressure	32	115.0	+2.4	3.22	0.57	4.28***	115.5	+4.3	5.23	0.93	4.70***
Diastolic pressure	32	67.0	+3.5	4.20	0.74	4.67***	66.9	+6.0	5.05	0.89	6.69***
Pulse pressure	32	48.0	−1.0	3.83	0.68	1.52	48.6	−1.6	4.50	0.80	2.04*
Heart rate	30	63.1	+11.7	8.56	1.56	7.47***	64.0	+9.3	6.29	1.15	8.12***
Stroke volume	30	111.0	−6.5	9.13	1.67	3.92***	115.2	−7.0	7.75	1.41	4.97***
Cardiac output	30	6.96	+0.78	0.89	0.16	4.82***	7.31	+0.55	0.81	0.15	3.60***

Tests IA, IB, IIA and IIB are further described in the text; this system of numbering is used throughout the tables for Series F.
*P < 0.05
**P < 0.01
***P < 0.001
Abbreviations: S.D. = standard deviation; S.E.M. = standard error of the mean.

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From further examination of Series F, it is possible to study the effect of several factors on the circulatory response to smoking.

The influence of time of day: The effect of time of day on the control readings may be seen in the upper part of Table III where the means of the paired differences are compared with their variances to give t values as tests of significance. On the first day (IA-IB), although all the differences are negative, i.e., the control values are higher before lunch than before breakfast, none of these differences is statistically significant. On the second day (IIA-IIB), however, all the prelunch readings are significantly higher than the prebreakfast readings excepting the diastolic pressure which is virtually the same in the two groups.

Similar statistical comparisons made of the change produced by smoking one cigarette, are set forth in the lower half of Table III. These results are complementary to those above. On the first day (IA-IB) there is a greater response to smoking before breakfast, although in only one measurement—the systolic pressure—is the change significant at the 5 per cent level. On the second day (IIA-IIB) systolic and pulse pressure, heart rate, and cardiac output show a bigger rise before breakfast. These findings tally with the subjective observation by many smokers that the first cigarette in the morning has more effect than any other, especially if it is smoked in the fasting state.

TABLE III. MEAN DIFFERENCES IN CONTROL VALUES AND IN CHANGES ON SMOKING (SERIES F)

MEASUREMENT	IA–IB		IIA–IIB		IA–IIA		IB–IIB	
	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t
Control value								
Systolic pressure	−1.78	1.96	−2.59	2.91**	+0.31	0.21	−0.50	0.39
Diastolic pressure	−0.66	0.61	+0.03	0.05	−0.66	0.39	+0.03	0.02
Pulse pressure	−1.12	1.04	−2.62	2.92**	+0.97	0.58	−0.53	0.34
Heart rate	−2.23	1.97	−4.00	3.24**	+0.80	0.68	−0.97	0.69
Stroke volume	−1.57	0.72	−4.57	2.74*	−1.23	0.42	−4.23	2.11*
Cardiac output	−0.38	2.03	−0.71	4.39***	−0.03	0.14	−0.36	1.77
Change after smoking								
Systolic pressure	+2.94	2.48*	+2.19	2.52*	−1.16	0.88	−1.91	2.36*
Diastolic pressure	+1.59	1.40	−0.09	0.12	−0.81	0.67	−2.50	2.87**
Pulse pressure	+1.34	1.16	+2.28	2.36*	−0.34	0.29	+0.59	0.63
Heart rate	+1.67	1.17	+3.97	2.52*	+0.03	0.02	+2.33	1.66
Stroke volume	+0.37	0.16	+1.53	0.68	−0.67	0.27	+0.50	0.27
Cardiac output	+0.25	1.62	+0.54	3.14**	−0.07	0.35	+0.23	1.50

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

We have commented above that the "control" and "change" figures are complementary, and, in fact, the "final" figures (or absolute readings after smoking) are quite remarkably constant (Table IV and Fig. 1). When "t" tests on the paired differences are examined on the null hypothesis, the only difference from zero which is significant is the stroke volume on the second day (Table V).

TABLE IV. COMPARISON OF MEANS OF CONTROL VALUES, CHANGES AND FINAL VALUES IN SERIES F SMOKING TESTS

MEASUREMENT	BEFORE BREAKFAST		BEFORE LUNCH	
	FIRST DAY	SECOND DAY	FIRST DAY	SECOND DAY
	IA	IIA	IB	IIB
Systolic pressure				
Control	113.2	112.9	115.0	115.5
Change	+ 5.4	+ 6.5	+ 2.4	+ 4.3
Final	118.6	119.4	117.4	119.8
Diastolic pressure				
Control	66.3	67.0	67.0	66.9
Change	+ 5.1	+ 5.9	+ 3.5	+ 6.0
Final	71.4	72.8	70.4	72.9
Pulse pressure				
Control	46.9	45.9	48.0	48.6
Change	+ 0.3	+ 0.7	− 1.0	− 1.6
Final	47.2	46.6	47.0	46.9
Heart rate				
Control	60.8	60.0	63.1	64.0
Change	+13.3	+13.3	+11.7	+ 9.3
Final	74.2	73.3	74.7	73.4
Stroke volume				
Control	109.4	110.6	111.0	115.2
Change	− 6.2	− 5.5	− 6.5	− 7.0
Final	103.2	105.1	104.4	108.2
Cardiac output				
Control	6.57	6.60	6.96	7.31
Change	+ 1.03	+ 1.10	+ 0.78	+ 0.55
Final	7.60	7.70	7.74	7.86

The adaptation factor: Since the IA test was the first smoking test performed on each of these subjects, it might be thought that on that occasion the subjects would be somewhat tense or apprehensive and that they would be more relaxed during subsequent tests. We have called the effects of familiarity with the test the "adaptation factor." This factor will be studied more closely and over a longer period in the analysis of Series E. In Series F, however, we can note what differences, if any, exist between the first and the second day. In the control values (Table III, IA-IIA, and IB-IIB) only the prelunch stroke volume is significantly different at the 5 per cent level. Comparison of the effect of smoking shows that the rises in systolic and diastolic pressures are significantly greater on the second day before lunch (Table III). None of the other differences is significant. Comparing the final figures shows no significant differences, although the trends are absolutely uniform: pulse pressures and heart rates are higher on the first than on the second day, while the other measurements are lower (Table V). It appears then that adaptation is an unimportant factor in the smoking test, a view which is confirmed in Series E.

Effects of smoking habits: An attempt has been made to see whether or not smoking habits influence either the control levels or the response to smoking. Statistically, this factor would be best studied as a regression. Not all the subjects were cigarette smokers, however, and it is difficult if not impossible to express an exact equivalent in cigarettes for the number of cigars or the amount of pipe tobacco smoked. It was, therefore, decided to divide the subjects into "lighter" and "heavier" smokers, the dividing line for cigarettes being 10 per day. By a fortunate chance the cigar and pipe smokers readily fell into this

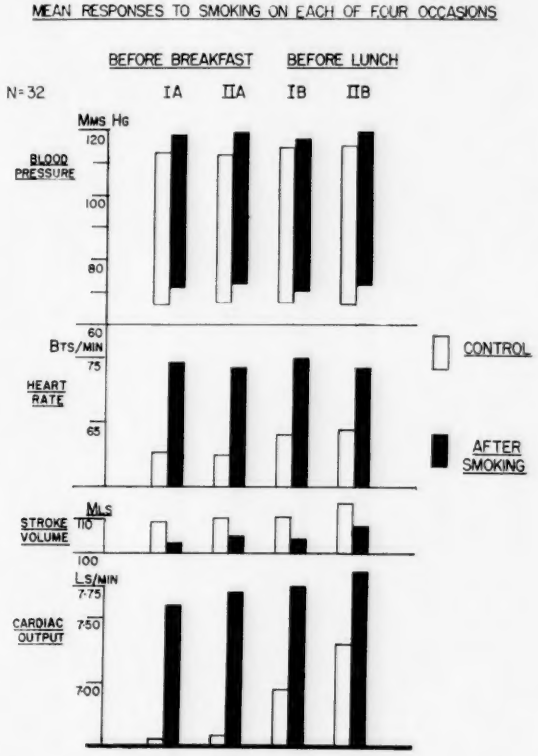

Fig. 1.—The relative constancy of the final postsmoking values under different circumstances. In order to represent small differences, only the upper portions of the columns for heart rate, stroke volume, and cardiac output are shown. For this reason, changes on smoking appear exaggerated.

classification, being all obviously very heavy or very light smokers. The division of subjects gave 12 lighter and 20 heavier smokers; as these numbers are small and any differences are also small, the results of all four tests were pooled for each smoking habit group, giving for the lighter smokers 48 complete sets of results and for the heavy smokers 80 sets of blood pressure readings and 72 sets of cardiac measurements (since both subjects with incomplete ballistocardiographic data were heavy smokers). The numbers of degrees of freedom in the comparisons between these two groups are to all intents and purposes infinitely large. Nothing was lost by pooling, since it transpired that the mean variance

TABLE V. PAIRED DIFFERENCES BETWEEN FINAL VALUES IN FOUR SMOKING TESTS (SERIES F)

FINAL MEASUREMENTS	IA–IB		IIA–IIB		IA–IIA		IB–IIB		IA–IIB		IIA–IB	
	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t	MEAN DIFFERENCE	t
Systolic pressure	+1.16	0.87	−0.41	0.43	−0.84	0.48	−2.41	1.88	−1.25	0.68	+2.00	1.55
Diastolic pressure	+0.94	1.27	−0.06	0.07	−1.47	0.71	−2.47	1.41	−1.53	0.83	+2.41	1.24
Pulse pressure	+0.22	0.17	−0.34	0.34	+0.62	0.39	+0.06	0.04	+0.28	0.16	−0.41	0.27
Heart rate	−0.57	0.46	−0.03	0.02	+0.83	0.67	+1.37	0.88	+0.80	0.65	−1.40	0.71
Stroke volume	−1.20	0.79	−3.03	2.29*	−1.90	1.12	−3.73	1.92	−4.93	2.36*	+0.70	0.41
Cardiac output	−0.13	0.87	−0.17	0.95	−0.09	0.05	−0.13	0.71	−0.26	1.41	−0.04	0.17

*P < 0.05.

in the pooled group in each instance was very little more than that for the individual group of tests. It is clear, then, that the standard error was little more than half as great (since the number of observations is four times as great and the standard error varies inversely as the square root of the number of observations). The results obtained, set forth in Table VI, do not show much difference between the two groups. Lighter smokers have almost always higher control values and show less change on smoking. The results in the final figures are

TABLE VI. THE EFFECTS OF SMOKING HABITS ON THE RESULTS OF THE SMOKING TESTS (SERIES F)

MEASUREMENT	LIGHT SMOKERS (L) MEAN	HEAVY SMOKERS (H) MEAN	L–H	t
Systolic pressure				
Control	116.65	112.66	+ 3.99	2.910**
Change	+ 3.44	+ 5.41	− 1.97	1.910
Final	120.08	118.08	+ 2.01	1.079
Diastolic pressure				
Control	67.79	66.20	+ 1.59	1.144
Change	+ 4.96	5.18	− 0.22	0.227
Final	72.75	71.38	+ 1.37	0.723
Pulse pressure				
Control	48.85	46.46	+ 2.39	1.737
Change	− 1.52	+ 0.24	− 1.76	2.350*
Final	47.33	46.70	+ 0.63	0.418
Heart rate				
Control	63.92	60.71	+ 3.21	2.088*
Change	+ 9.98	+13.19	− 3.21	1.720
Final	73.90	73.90	0.00	0.000
Stroke volume				
Control	110.33	112.36	− 2.03	0.689
Change	− 5.81	− 6.64	+ 0.83	0.493
Final	104.52	105.72	− 1.20	0.451
Cardiac output				
Control	7.03	6.75	+ 0.28	1.315
Change	+ 0.65	+ 1.01	− 0.36	1.863
Final	7.68	7.76	− 0.08	0.323

Where in the above comparisons variance is significantly different in the two groups, probability values are calculated from weighted t values (Cochran's technique).

* $P < 0.05$.
** $P < 0.01$.

much more evenly distributed and none of the differences reaches the significant level. There are no grounds for pairing the individual subjects, but if we compare the mean values for lighter and heavier smokers in tests IA, IB, IIA, and IIB separately, we can study consistency of trends. The results so obtained are laid out in Table VII. This shows, for example, that in all four tests (IA, IB, IIA, and IIB) the lighter smokers had a higher average control heart rate and a smaller average rise in heart rate on smoking, but that the average final heart rate was higher in two instances and lower in the other two.

TABLE VII. CONSISTENCY OF TRENDS OF MEAN VALUES IN THE FOUR GROUPS OF TESTS COMPARING THE LIGHTER AND HEAVIER SMOKERS (SERIES F)

MEASUREMENT	CONTROL		CHANGE		FINAL	
	LIGHTER SMOKERS	HEAVIER SMOKERS	LIGHTER SMOKERS	HEAVIER SMOKERS	LIGHTER SMOKERS	HEAVIER SMOKERS
Systolic pressure	4	0	1	3	3	1
Diastolic pressure	3	1	1	3	2	2
Pulse pressure	3	1	0	4	2	2
Heart rate	4	0	0	4	2	2
Stroke volume	1	3	3	1	1	3
Cardiac output	4	0	0	4	1	3

The numbers in Tables VII indicate in how many of the four groups of comparisons the mean value is the higher (in the direction of positivity) in the group concerned.

From the four such comparisons that can be made, it is possible to obtain only an over-all impression: that in the main the control values are higher more frequently in the lighter smokers, the change greater in the heavier smokers, and the final readings evenly distributed.

Effect of exercise habits: Since it is difficult to quantitate every-day exercise accurately, in studying its effect upon the response to smoking we have made a broad division as in the preceding section. Inquiry into the amount and kind of exercise during the preceding month was made at the time of each smoking test and the subjects classified as taking "no," "little," "moderate," or "much" exercise according to prearranged definitions. Two main groups were then formed by combining those taking no and little exercise on the one hand and moderate and much on the other. The resulting groups were of equal size. As before, the A and B tests were pooled with the same advantage from the reduction in size of the standard errors with little ill effect from slight loss of homogeneity of the material. The resulting groups are compared by mean values (Table VIII). The differences are not great: the less active subjects have a higher resting heart rate with a bigger rise on smoking and this is reflected in a greater rise and a higher final figure for the cardiac output. Other differences are not statistically significant.

It might be thought that the factors of smoking habits and exercise might influence each other: that the more athletic students are more sociable and more likely to smoke heavily; or conversely, that many of them are likely to be light smokers as a result of athletic training. In this way one would be comparing two groups, the composition of which differs in more than one respect. Accordingly, the association between these two factors has been analyzed (Table IX). It is clear that even if we look upon all the tests as having been performed on different individuals instead of four of them by each, the value for chi-square is not significant at the 5 per cent level, though it does seem that the less athletic subjects smoke more.

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TABLE VIII. THE EFFECTS OF EXERCISE HABITS ON THE RESULTS OF THE SMOKING TEST (SERIES F)

MEASUREMENT	LIGHT EXERCISE (L) MEAN	HEAVY EXERCISE (H) MEAN	L–H	t
Systolic pressure				
Control	113.48	114.83	−1.34	1.003
Change	4.06	5.28	−1.22	1.215
Final	117.55	120.11	−2.56	1.623
Diastolic pressure				
Control	65.58	68.02	−2.44	1.887
Change	4.64	5.55	−0.91	0.997
Final	70.22	73.56	−3.34	1.917
Pulse pressure				
Control	47.91	46.81	1.09	0.816
Change	− 0.58	− 0.27	−0.31	0.404
Final	47.33	46.55	0.78	0.542
Heart rate				
Control	63.42	60.36	3.06	2.038*
Change	13.47	10.12	3.34	1.940
Final	76.89	70.48	6.41	3.093**
Stroke volume				
Control	109.55	113.84	−4.29	1.502
Change	− 4.97	− 7.84	2.87	1.780
Final	104.58	106.00	−1.42	0.545
Cardiac output				
Control	6.89	6.82	0.07	0.358
Change	1.11	0.59	0.52	2.927**
Final	8.00	7.41	0.59	2.633*

Where in the above comparisons variance is significantly different in the two groups, probability values are calculated from weighted t values (Cochran's technique).

* $P < 0.05$.

** $P < 0.01$.

TABLE IX. CORRELATION BETWEEN THE EXERCISE AND SMOKING HABITS OF THE SUBJECTS

EXERCISE HABITS	SMOKING HABITS				TOTAL
	HEAVY SMOKERS		LIGHT SMOKERS		
	OBS.	EXP.	OBS.	EXP.	
Much	36	40	28	24	64
Little	44	40	20	24	64
Total	80		48		128

$\chi_1^2 = 1.633$ $p < 0.2$

The constancy of ceiling: One interesting fact that emerged from this analysis is that the final figure immediately after smoking was the most constant reading (Table IV, Fig. 1). These "ceiling" values varied so little that even if

TABLE X. VARIABILITY OF INDIVIDUAL RESPONSE TO SMOKING: MEAN VALUES AND STANDARD DEVIATIONS OF CIRCULATORY MEASUREMENTS IN EIGHT TESTS ON EACH OF SIX SUBJECTS (SERIES E)

SUBJECT NO.	VALUE	SYSTOLIC PRESSURE		DIASTOLIC PRESSURE		PULSE PRESSURE		HEART RATE		STROKE VOLUME		CARDIAC OUTPUT	
		MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
58127	Control	125.8	3.2	65.8	6.2	60.0	6.0	52.1	3.6	110.8	7.7	5.8	0.5
	Change	+12.5**	7.0	+12.2***	3.0	+ 0.2	6.9	+17.2***	5.3	− 4.3	12.2	+1.6**	1.0
	Final	138.3	7.9	78.0	4.4	60.2	6.3	69.3	2.8	106.5	8.6	7.4	0.7
58158	Control	110.9	3.6	65.6	3.0	45.2	4.7	69.8	7.7	99.7	8.9	6.9	0.7
	Change	+ 2.9	3.6	+ 7.0***	1.7	− 4.1*	4.8	+19.1***	4.9	− 9.5**	7.3	+1.1***	0.4
	Final	113.8	3.1	72.6	2.6	41.1	3.6	88.9	5.7	90.2	4.6	8.0	0.6
59170	Control	94.4	3.7	61.0	1.7	33.4	3.1	66.9	4.7	120.1	6.5	8.0	0.7
	Change	0.0	2.0	+ 0.8	2.4	− 0.8	1.7	+ 5.5**	4.4	+ 2.3	10.7	+0.8**	0.5
	Final	94.4	3.9	61.8	3.0	32.6	2.9	72.4	7.8	122.4	11.4	8.8	0.7
58102	Control	145.0	3.8	79.1	4.4	65.9	4.7	65.9	4.7	134.4	9.9	8.8	0.6
	Change	+ 3.5	5.9	+ 4.6	5.4	− 1.1	5.1	+10.4***	5.2	− 6.6*	8.5	+0.9**	0.5
	Final	148.5	4.9	83.7	3.7	64.8	2.9	76.3	6.3	127.8	7.7	9.7	0.4
59118	Control	112.1	5.9	70.8	8.1	41.4	4.6	61.1	7.5	124.5	6.7	7.6	0.8
	Change	+ 0.9	6.0	+ 1.0	2.7	− 1.9	4.0	+ 1.8	3.0	− 3.2	7.4	0.0	0.6
	Final	111.2	5.0	71.8	8.8	39.5	5.6	63.0	6.4	121.3	5.6	7.6	0.8
58152	Control	116.8	5.4	71.5	4.0	45.2	5.3	72.7	4.6	99.2	3.6	7.2	0.4
	Change	+ 0.9	2.5	+ 3.4	5.5	− 2.5	5.7	+ 1.2	5.5	+ 0.5	7.1	+0.2	0.4
	Final	117.6	4.3	74.9	5.1	42.7	3.8	73.9	5.6	99.7	5.1	7.4	0.5
Mean	Control	117.5	4.4	69.0	5.1	48.5	4.8	64.8	5.7	114.8	7.5	7.4	0.6
	Change	+ 3.1	4.9	+ 4.8	3.8	− 1.7	5.0	+ 9.2	4.8	− 3.5	8.1	+0.8	0.6
	Final	120.6	5.1	73.8	5.0	46.8	4.4	74.0	6.0	111.3	7.5	8.2	0.7

The probability estimates, showing that the change on smoking is significant, are made from "t" tests which compare the mean change on smoking with the variability of the mean change on smoking.

S.D. = standard deviation.

*P < 0.05.

**P < 0.01.

***P < 0.001.

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the readings obtained under the most unlike circumstances are paired (i.e., those before breakfast on one day with those before lunch on the other) only two of the 36 combinations (5.6 per cent) are significantly different at the 5 per cent level—about the frequency one would expect by chance (Table V). This observation suggests that smoking a cigarette tends to push the various measurements to a ceiling, as if a cigarette at different times of day "takes up the slack" regardless of the control figure. Moreover, the ceiling was essentially the same for lighter and heavier smokers, and differences in habits of exercise did not affect it.

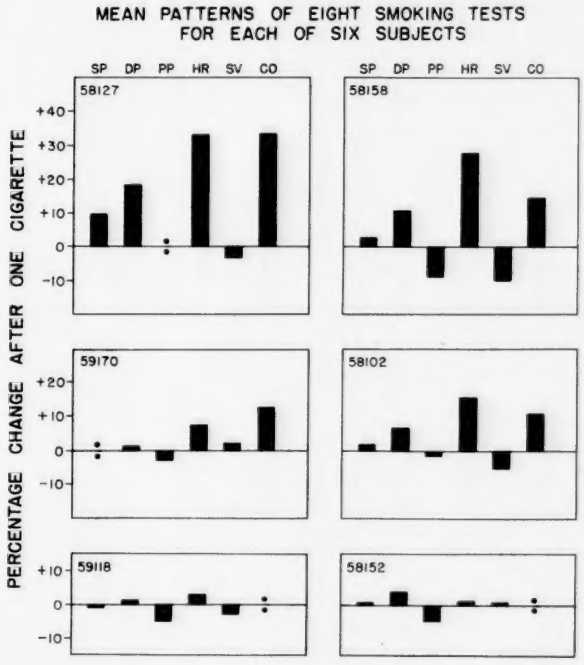

Fig. 2.—The individual circulatory response to smoking. Each column represents the mean of the changes in eight tests. The subjects are arranged in order of reactivity. The same order is used in Table X and Fig. 3.

The reproducibility and individuality of the measurements on repeated tests on subjects under standardized conditions: the series of eight tests on each of 6 subjects (*Series E*).—The results obtained are summarized in Table X which shows the average and standard deviation for each function measured in the six subjects on eight occasions. The bottom row shows the means of the 48 readings for each function with a mean of individual standard deviation (calculated as root mean variance). Fig. 2 shows the mean response to smoking of each subject. The results of repeated tests indicate that: (1) on the average, individual characteristics were maintained throughout the series of tests; (2) persons of varying degrees of reactivity, from marked (Subject 58127) to slight (Subject 58152), were represented among the test subjects. As might be expected, when

the subjects are arranged in order of decreasing responsiveness, most of the mean changes which are significantly greater than the standard deviations appear in the upper portion of the table (Table X).

From the average standard deviations, we have attempted to estimate the reliability of a single test on one subject, by taking twice this value as the 95 per cent confidence limits (Table XI). Thus the control reading for the systolic pressure, for example, in one test on a given subject will lie within 8.8 mm. Hg either way of the population mean for that person, provided that: (1) one such test is an unbiased estimate of the mean; and (2) differences between the variances of the several individuals are entirely explicable by chance and do not denote that some subjects are more variable in their response than others.

TABLE XI. CONFIDENCE LIMITS ON THE RESULTS OF A SINGLE TEST (SERIES E)

MEASUREMENT	MEAN STANDARD DEVIATION (ROOT MEAN VARIANCE)	MEAN MEAN	95% CONFIDENCE LIMITS (ABSOLUTE)
Systolic pressure			
Control	4.4	117.5	± 8.8
Change	4.9	+ 3.1	± 9.8
Final	5.1	120.6	±10.2
Diastolic pressure			
Control	5.1	69.0	±10.2
Change	3.8	+ 4.8	± 7.6
Final	5.0	73.8	±10.0
Pulse pressure			
Control	4.8	48.5	± 9.6
Change	5.0	− 1.7	±10.0
Final	4.4	46.8	± 8.8
Heart rate			
Control	5.7	64.8	±11.4
Change	4.8	+ 9.2	± 9.6
Final	6.0	74.0	±12.0
Stroke volume			
Control	7.5	114.9	±15.0
Change	9.1	− 3.6	±18.2
Final	7.5	111.3	±15.0
Cardiac output			
Control	0.6	7.4	± 1.2
Change	0.6	+ 0.8	± 1.2
Final	0.7	8.2	± 1.4

That the first premise is a valid assumption is seem in Table XII, where the results of the set of six first tests are averaged, then the second tests, the third, and so on. The averages of the first tests differ very little from the averages of the subsequent tests and are a very good estimate of the mean for all 48 tests. Similar results are obtained if the results are ranked. The second premise has been examined by Bartlett's test for homogeneity of variance, the results being presented in Table XIII. In 13 of the readings, differences appear to be no more than could be readily explained by chance. In the other five, including all three

TABLE XII. COMPARISON OF THE MEAN VALUES OF EIGHT SETS OF TESTS (SERIES E)

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH	ALL
Systolic pressure									
Control	119.7	115.3	116.2	118.5	119.5	119.2	114.2	117.3	117.5
S.D.	18.1	14.3	15.1	18.6	17.0	16.7	19.6	19.0	16.2
Change	1.0	6.0	3.2	3.0	2.5	3.7	4.2	1.7	3.1
S.D.	4.0	2.3	5.7	8.5	9.4	9.7	7.5	2.7	6.5
Final	120.7	121.3	119.3	121.5	122.0	122.8	118.3	119.0	120.6
S.D.	17.8	15.5	20.5	22.8	20.6	22.9	21.0	19.4	18.7
Diastolic pressure									
Control	70.2	67.8	67.2	68.8	69.2	70.8	68.8	68.8	69.0
S.D.	8.8	6.3	7.7	7.1	6.5	7.3	11.8	7.4	7.5
Change	4.3	6.3	7.5	5.2	4.3	5.2	2.0	3.8	4.8
S.D.	6.2	5.8	4.5	6.7	5.3	5.4	5.6	3.2	5.3
Final	74.5	74.2	74.7	74.0	73.5	76.0	70.8	72.7	73.8
S.D.	8.4	5.3	10.5	7.3	7.6	8.3	12.5	8.9	8.3
Pulse pressure									
Control	49.5	47.5	49.0	49.7	50.3	48.3	45.3	48.5	48.5
S.D.	16.4	14.0	11.0	15.3	11.3	11.8	10.4	12.4	12.1
Change	−3.3	−0.3	−4.3	−2.2	−1.8	−1.5	2.2	−2.2	−1.7
S.D.	5.1	4.5	5.5	5.2	6.5	5.2	3.8	2.5	4.9
Final	46.2	47.2	44.7	47.5	48.5	46.8	47.5	46.3	46.8
S.D.	12.4	11.1	12.0	16.8	14.6	16.2	12.1	10.8	12.5
Heart rate									
Control	63.3	66.8	64.5	64.6	69.0	63.4	60.5	66.1	64.8
S.D.	10.4	6.1	9.1	8.3	11.9	8.8	10.3	5.1	8.6
Change	8.7	9.2	7.6	11.1	8.0	9.6	10.4	9.2	9.2
S.D.	8.5	8.8	12.0	6.1	7.5	10.8	9.4	7.8	8.4
Final	72.0	76.0	72.1	75.7	77.0	73.0	70.9	75.2	74.0
S.D.	14.4	9.5	11.6	9.5	9.6	8.0	10.8	7.7	9.8
Stroke volume									
Control	116.7	116.2	114.1	113.0	115.4	116.1	114.3	112.4	114.8
S.D.	17.1	15.8	19.3	15.7	22.6	13.3	8.2	11.2	14.8
Change	−0.5	−2.6	−2.5	−2.3	−4.4	−8.0	−5.8	−1.7	−3.5
S.D.	12.4	10.9	9.9	11.3	8.7	9.0	10.7	5.0	9.5
Final	116.2	113.6	111.6	110.6	111.0	108.1	108.4	110.7	111.3
S.D.	19.5	15.4	20.1	17.5	18.4	13.2	15.7	9.4	15.4
Cardiac output									
Control	7.34	7.77	7.32	7.27	7.60	7.35	6.90	7.42	7.40
S.D.	1.30	1.24	1.24	1.18	1.15	1.28	1.18	0.87	1.13
Change	0.83	0.83	0.57	0.99	0.64	0.54	0.73	0.90	0.75
S.D.	0.75	0.64	1.18	1.26	0.61	0.55	0.72	0.73	0.79
Final	8.18	8.60	7.90	8.26	8.44	7.89	7.63	8.32	8.15
S.D.	1.08	1.29	0.88	0.71	1.07	1.27	1.31	1.04	1.06

S.D. = Standard deviation.

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diastolic readings, individual subjects seem to differ widely. Moreover, our main concern is with the change on smoking, and it transpires that the variability of the *change* of all three blood pressure readings, systolic, diastolic, and pulse pressure, differs significantly from individual to individual.

TABLE XIII. BARTLETT'S TEST FOR HOMOGENEITY OF VARIANCE IN THE DATA FROM SERIES E

MEASUREMENT	M′	p
Systolic pressure		
Control	4.206	0.75
Change	14.557*	0.025
Final	7.206	0.25
Diastolic pressure		
Control	16.885**	0.005
Change	13.99*	0.025
Final	14.107*	0.025
Pulse pressure		
Control	2.857	0.75
Change	11.263*	0.05
Final	7.524	0.25
Heart rate		
Control	6.072	0.5
Change	2.777	0.75
Final	6.211	0.5
Stroke volume		
Control	6.821	0.25
Change	3.958	0.75
Final	8.227	0.25
Cardiac output		
Control	3.499	0.75
Change	8.399	0.25
Final	3.912	0.75

M′ = Bartlett's index for homogeneity of variance (M), corrected for small sample size. A significant value for M′ indicates that variance differs from one subject to another. It is read as a χ^2 value (degrees of freedom: $6-1=5$).

* $P < 0.05$. **$P < 0.01$.

It seems then that our confidence limits may be applied to the first smoking test, and, in an individual test, probably to the heart rate, stroke volume, and cardiac output, but not to the blood pressure values. In other words, not only the mean, but also the variance is an individual characteristic: for some subjects, our confidence limits are too broad, and for others, too narrow. We have no way of predicting which of these errors is likely in any particular subject; regressions of variance on the mean show no significant correlation. In the main, of course, we will be able to distinguish "hypo-" from "hyper-" reactors, but from time to time we may make errors, and it is perhaps best to apply our confidence limits, especially for the blood pressure responses, to groups only. A standard error is easily computed from our confidence limits.

The object of the smoking test is to characterize a given subject according to the degree and direction of change in regard to each variable, and the success

of the test depends on the contrast between individual variation (intraindividual) on repeated tests and variation between individuals (interindividual). A single test is reliable if the intraindividual scatter is relatively small compared with the interindividual variation, but if there is not much difference between the intra- and interindividual variation, then the test will be of little value as a screening procedure. This question is best answered by an analysis of variance (Fig. 3).

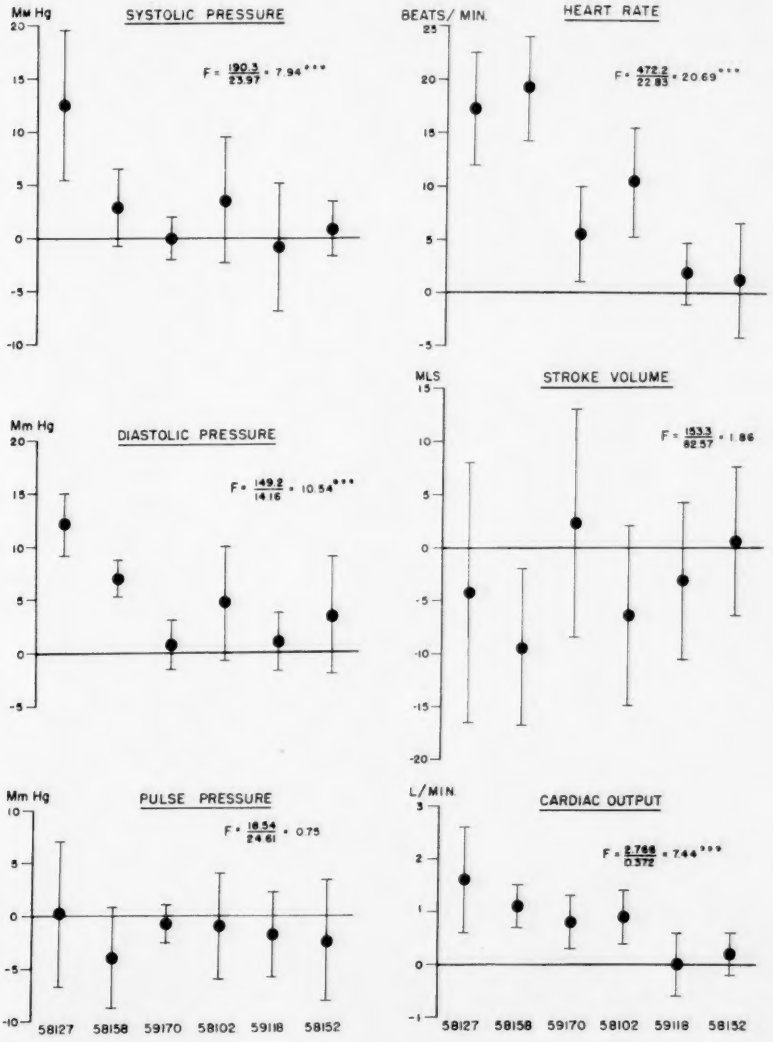

Fig. 3.—Intraindividual variation in eight smoking tests on each of 6 subjects. In each instance, the black circle marks the mean value and the lines one standard deviation above and below it. F represents the ratio of interindividual to intraindividual variance and is an indication of the confidence with which subjects may be classified according to the magnitude of the response. ***P <0.001.

Since we are chiefly concerned with *change* on smoking, the data concerning individuality of resting values, which is a matter of common experience, will not be presented here.

The variance obtained by pooling all 48 sets of readings of the change in systolic pressure after smoking, for example, arises from two sources: intraindividual variation as shown in Table X and interindividual variation which is found by subtracting the intraindividual variation from the total variation. We can then set up an analysis of variance as follows:

Source of variation	*Degrees of freedom*	*Sum of squares*	*Mean square*
Interindividual	$6-1=5$	951	190.3
Intraindividual	$6\ (8-1)=42$	1007	23.97
Total	$(6\times 8)-1=47$	1958	—

The ratio of the two mean squares (interindividual variation being always the numerator) is designated "F" and corresponding values for p are obtained from appropriate tables with (5,42) degrees of freedom. The value for F in this example is 7.94 which gives $p < 0.001$. From analyses similar to this we find that changes in systolic and diastolic pressure, heart rate, and cardiac output are fairly individual, and are likely to produce a satisfactory subdivision of our subjects, whereas changes in pulse pressure and stroke volume are not, except perhaps in rare instances. These findings agree with our previous general impressions.

TABLE XIV. COMPARISON OF VARIANCE IN THE CONTROL AND FINAL FIGURES IN SERIES E

SUBJECT NO.	VALUE	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	PULSE PRESSURE	HEART RATE	STROKE VOLUME	CARDIAC OUTPUT
58127	Control	10.00	38.86	36.57	13.33	58.60	0.284
	Final	62.29	19.71	40.29	7.95	74.74	0.519
	r	−0.77*	+0.61	−0.05	+0.27	−0.12	−0.30
58158	Control	13.29	9.12	21.93	59.30	80.04	0.454
	Final	9.36	6.86	12.70	31.98	21.03	0.398
	r	+0.19	+0.25	+0.28	+0.44	+0.66	+0.10
59170	Control	13.43	2.86	9.71	22.14	41.89	0.490
	Final	15.14	8.86	8.57	61.52	128.86	0.507
	r	−0.12	−0.59	+0.12	−0.73*	−0.54	−0.03
58102	Control	14.57	19.27	22.13	21.74	98.12	0.353
	Final	24.00	13.36	8.50	39.06	58.64	0.176
	r	−0.25	+0.18	+0.45	−0.34	+0.30	+0.38
59118	Control	34.70	65.64	21.13	55.81	44.68	0.628
	Final	25.36	77.93	31.71	41.43	30.88	0.714
	r	+0.17	−0.27	−0.28	+0.35	+0.19	−0.11
58152	Control	28.79	16.00	28.64	21.13	12.83	0.160
	Final	18.27	26.14	14.21	31.29	26.21	0.267
	r	+0.44	−0.25	+0.33	−0.21	−0.36	−0.31

*P < 0.05. r = correlation coefficient.

It is of some interest to compare the variability of the control and the final readings in Series E. The variances for each kind of measurement are set forth in Table XIV. The most sensitive way of detecting differences between these two readings is by Pitman's technique, which is designed for comparing the variances of paired measurements.[3] Only two of the 36 correlation coefficients so obtained are significant at the 5 per cent level, and since this is about what would be expected to occur by chance, there is no evidence that final readings in Series E are any less variable than the control readings. This marked contrast to what was found in Series F remains to be explained but may will lie in the different test conditions of Series E and Series F: in Series E, all eight control readings were made at a single time of day, whereas in Series F, two control readings were obtained before breakfast and two before lunch under somewhat different conditions.

Comparison between the Results Obtained in the Different Series of Smoking Tests.—We have thus far considered the reproducibility of the results under rigorously standardized conditions and also some of the factors which seem to influence the size of the response. It now remains to compare the results obtained with the different degrees of standardization of the test conditions to seen if in fact these materially affect the results.

In Table XV the variances in Series O and Series F are compared. In each instance the variance in the former is divided by that in the latter, the significance of the F value so obtained being read from two-tailed tables. If the values are significantly greater than one then the variance is significantly greater in the O Series while if significantly less than one the converse is true. It is apparent that of the 72 values obtained, 19 are significantly different from one, 8 of them at the 1 per cent level. Notwithstanding these marked differences, there is no readily recognizable pattern in the results: in 10 instances, the variance is significantly greater than one (6 at the 5 per cent level and 4 at the 1 per cent level of probability) and in 9 significantly less than one (5 at the 5 per cent level and 4 at the 1 per cent level). There appears to be a definite trend: most of the 5 per cent and all of the 1 per cent probabilities in which the Series O reading is greater are seen to occur in the blood pressure readings, and the converse appears for the heart rate, stroke volume, and cardiac output. These comparisons of variance are of more importance in comparing the mean values, since in the appropriate cases it is necessary to calculate "t" values by Cochran's technique, for comparing two groups of unequal numbers and significantly different variances. In Table XVI we have computed the algebraic differences between the means of the 69 single tests on the one hand and those of the four sets of tests in Series F on the other. The significance of these differences is indicated in the usual way. There is no very striking pattern, but it does appear that where there is a significant difference, in most instances, the control readings are higher in Series O, the change on smoking higher in Series F, and the final readings about evenly distributed.

Series O is compared with the eight tests in Series E in Tables XVII and XVIII. The former compares the variances by the same method as in Table XV. Twenty-one of the 144 results are significantly different from unity: 14

TABLE XV. COMPARISON OF THE VARIANCE IN SERIES O AND F

MEASUREMENT	VARIANCE RATIOS			
	O / IA	O / IIA	O / IB	O / IIB
Systolic pressure				
Control	2.44**	1.30	1.65	1.18
Change	0.855	0.870	3.70**	1.33
Final	1.35	0.926	2.32*	1.01
Diastolic pressure				
Control	0.735	0.833	0.855	1.23
Change	0.800	0.763	1.37	0.952
Final	0.549*	0.485*	0.714	0.658
Pulse pressure				
Control	1.44	1.62	1.91*	1.34
Change	2.19*	2.47**	3.68**	2.23*
Final	1.87	1.88	1.51	1.11
Heart rate				
Control	1.60	1.88	2.03*	1.81
Change	0.452**	0.330**	0.654	1.21
Final	1.08	0.671	1.29	0.935
Stroke volume				
Control	1.01	1.08	0.990	1.09
Change	0.451**	0.490*	0.526*	0.730
Final	1.44	2.09*	1.40	1.33
Cardiac output				
Control	1.88	1.64	1.31	1.44
Change	0.543*	0.351**	0.714	0.847
Final	1.60	1.10	1.50	1.20

*P < 0.05. **P < 0.01.

of these (6 at the 5 per cent level and all 8 at the 1 per cent level) occurred in the systolic pressure readings, only 5 occurring in the remaining 120 values and all at the 5 per cent level. In almost all instances these values are significantly less than unity, a reflection of the fact that the groups of subjects being compared are of such unequal sizes (69 and 6, respectively) which means that the variance in group O has to be relatively very much larger to reach a significant level. Thus if we examine all readings other than systolic pressure, we find that 64 values are less than unity and 56 more. Again, however, in the systolic readings, only 4 of the 24 values are greater than unity. It seems, then, as if the only real difference in the two groups is that the systolic pressure is almost uniformly more variable between individuals in conditions standardized for each individual separately (but not uniform from one individual to another) than that within a large group of individuals under random conditions. The significance of this is obscure unless it be that there was a different observer in Series E (E.A.M.) or the fact that the latter subjects were in part selected. As before, we are mainly interested in using variance to assess the significance of differences in the mean values. It is clear from Table XVII that these are unimpressive.

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TABLE XVI. COMPARISON BETWEEN THE MEAN VALUES IN SERIES O AND F

MEASUREMENT	O–IA	O–IIA	O–IB	O–IIB	SIGNIFICANT DIFFERENCES	
					POSITIVE	NEGATIVE
Control						
Systolic pressure	1.0	1.3	−0.8	−1.3	0	0
Diastolic pressure	7.9***	4.6**	4.6**	4.7***	4	0
Pulse pressure	−4.3*	−3.3	−5.4**	−6.0***	0	3
Heart rate	10.0***	10.8***	7.7***	6.8**	4	0
Stroke volume	0.3	−0.9	−1.3	−10.5**	0	1
Cardiac output	1.12***	1.09***	0.73**	0.38	3	0
Change						
Systolic pressure	−2.8*	−3.9**	0.2	−1.7	0	2
Diastolic pressure	−0.2	−1.0	1.2	−1.1	0	0
Pulse pressure	−2.6*	−3.0**	−1.3	−0.7	0	2
Heart rate	−5.8**	−5.8*	−4.2*	−1.8	0	3
Stroke volume	2.4	1.7	2.7	3.2	0	0
Cardiac output	−0.56*	−0.63*	−0.31	−0.08	0	2
Final						
Systolic pressure	−1.8	−2.6	−0.6	−3.0	0	0
Diastolic pressure	5.1*	3.6	6.0**	3.6	2	0
Pulse pressure	−6.9***	−6.3**	−6.7***	−6.7**	0	4
Heart rate	4.2	5.0	3.5	5.0	0	0
Stroke volume	2.7	0.8	1.4	−2.3	0	0
Cardiac output	0.56*	0.46	0.42	0.30	1	0

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

These comparisons show that we have gained little by attempting to standardize the conditions of the test beyond those laid down for the original studies, of which Series O was a part.[1] The presence or absence of the fasting state appears to be the only factor of general importance.

Discussion: While many of the inferences to be drawn from the facts presented in the foregoing section have been mentioned, certain points deserve emphasis. In both Series F and Series E, we have found that the circulatory changes on smoking as measured in the first test are an unbiased estimate of the mean: although the mean of the results in repeated tests would give more information than a single test, nevertheless the first test is as accurate and informative as any other single test. This conclusion fulfills a most important requirement for a test which is to be useful as a screening procedure. Moreover, an analysis of variance showed that the intraindividual variations of systolic pressure, diastolic pressure, heart rate, and cardiac output are significantly smaller than the interindividual variations. This separation is an even more important requisite for a screening test, because it makes it possible with fair confidence to assign subjects to one of several broad groups according to the magnitude and direction of the response. These findings support the view previously formed that individual differences in the patterns of circulatory change on smoking have

TABLE XVII. COMPARISON OF THE VARIANCE IN SERIES O AND E

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH
Systolic pressure								
Control	0.284*	0.452	0.408	0.267**	0.321*	0.332*	0.241**	0.258*
Change	2.28	7.02*	1.13	0.500	0.417	0.385	0.649	4.89
Final	0.316	0.422	0.239**	0.194**	0.250**	0.192**	0.228**	0.267**
Diastolic pressure								
Control	0.629	1.22	0.826	0.962	1.16	0.917	0.336*	0.893
Change	0.625	0.730	1.04	0.543	0.870	0.893	0.763	2.38
Final	0.840	2.10	0.538	1.11	1.07	0.862	0.380	0.752
Pulse pressure								
Control	0.323*	0.448	0.719	0.373	0.690	0.625	0.906	0.571
Change	1.74	2.27	1.47	1.67	1.07	1.66	3.18	7.31*
Final	0.671	0.840	0.719	0.362	0.481	0.392	0.704	0.877
Heart rate								
Control	1.14	3.33	1.74	1.78	0.877	1.60	1.16	4.77
Change	0.667	0.617	0.334*	1.28	0.625	0.415	0.543	0.794
Final	0.633	1.44	0.971	1.45	1.42	2.03	1.11	2.19
Stroke volume								
Control	0.855	1.00	0.676	1.02	0.490	0.662	3.74	2.00
Change	0.283*	0.369	0.444	0.342*	0.578	0.549	0.383	1.77
Final	0.704	1.25	0.735	0.971	0.885	1.71	1.20	3.38
Cardiac output								
Control	0.943	1.04	0.909	1.14	1.20	0.971	1.00	2.10
Change	1.01	1.34	0.405	0.360*	1.52	1.82	1.72	1.06
Final	1.79	1.25	2.71	4.18	1.80	1.29	1.10	1.93

These figures were obtained by dividing the variance in Series O by those in Series E.
*P < 0.05.
**P < 0.01.

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TABLE XVIII. COMPARISON OF THE MEANS IN SERIES O AND E

MEASUREMENT	FIRST	SECOND	THIRD	FOURTH	FIFTH	SIXTH	SEVENTH	EIGHTH
Systolic pressure								
Control	5.5	1.1	2.0	4.3	5.3	5.0	0.0	3.1
t	0.74	0.18	0.32	0.56	0.75	0.72	0.0	0.40
Rise	−1.6	3.4	0.6	0.4	−0.1	1.1	1.6	−0.9
t	0.89	2.79*	0.25	0.11	0.03	0.27	0.51	0.68
Final	3.9	4.5	2.5	4.7	5.2	6.0	1.5	2.2
t	0.53	0.70	0.30	0.50	0.63	0.64	0.17	0.27
Diastolic pressure								
Control	−1.4	−3.8	−4.4	−2.8	−2.4	−0.8	−2.8	−2.8
t	0.38	1.40	1.35	0.92	0.86	0.26	0.57	0.89
Rise	−0.6	1.4	2.6	0.3	−0.6	0.3	−2.9	−1.0
t	0.23	0.58	1.27	0.11	0.27	0.13	0.39	0.70
Final	−2.0	−2.3	−1.8	−2.5	−3.0	−0.5	−5.6	−3.8
t	0.56	0.97	0.41	0.80	0.94	0.14	1.08	1.01
Pulse pressure								
Control	6.9	4.9	6.4	7.1	7.7	5.7	2.7	5.9
t	1.01	0.84	1.38	1.12	1.62	1.15	0.61	1.14
Rise	−1.0	2.0	−2.0	0.1	0.4	0.8	4.5	0.1
t	0.48	1.01	0.83	0.04	0.14	0.35	2.60*	0.08
Final	5.9	6.9	4.4	7.2	8.2	6.6	7.2	6.0
t	1.13	1.47	0.87	1.03	1.35	0.98	1.42	1.31
Heart rate								
Control	−7.5	−3.9	−6.3	−6.2	−1.8	−7.4	−10.3	−4.7
t	1.69	1.38	1.71	1.70	0.36	1.94	2.34	1.89
Rise	1.2	1.7	0.1	3.6	0.5	2.1	2.9	1.7
t	0.34	0.46	0.02	1.36	0.14	0.47	0.74	0.52
Final	−6.3	−3.2	−6.2	−3.4	−1.3	−5.3	−7.4	−3.1
t	1.06	0.77	1.26	0.83	0.31	1.49	1.60	0.90
Stroke volume								
Control	7.0	6.5	4.4	3.1	5.7	6.4	4.7	2.7
t	0.97	0.97	0.52	0.47	0.61	0.79	1.22	0.55
Rise	3.3	1.2	1.3	1.5	−0.6	−4.2	−2.0	2.1
t	0.64	0.26	0.33	0.32	0.16	1.12	0.45	0.96
Final	10.3	7.7	5.7	4.7	5.1	2.2	2.5	4.8
t	1.19	1.16	0.67	0.63	0.66	0.38	0.37	1.10
Cardiac output								
Control	−0.35	−0.80	−0.37	−0.42	−0.09	−0.35	−0.79	−1.27
t	0.64	1.52	0.75	0.83	0.02	0.64	1.47	3.29*
Rise	0.36	0.36	0.10	0.52	0.17	0.07	0.26	0.43
t	1.14	1.29	0.20	1.01	0.65	0.29	1.04	1.39
Final	0.02	0.44	−0.26	0.10	0.28	−0.27	−0.53	0.16
t	0.04	0.79	0.65	0.30	0.59	0.49	0.90	0.35

In each instance the O value was subtracted from the E value.
*$P < 0.05$.

real meaning and are not artefacts due to variance. It is worth noting, however, that the scatter of the results within the individual varies appreciably from subject to subject, so that confidence limits may be safely applied to groups only.

On repeated tests, the changes after smoking which characterized the 6 subjects in Series E were, in descending order of effectiveness, heart rate, diastolic pressure, systolic pressure, and cardiac output. Changes in pulse pressure and stroke volume did not provide good separation for these 6, but might do so for

larger and more representative groups. It was previously shown that there was quite good correlation between the pattern of response to smoking and the family history regarding hypertension or coronary disease.[1] As a group, subjects with parental hypertension showed a significantly greater rise in cardiac output than expected, while stroke volume and cardiac output were significantly smaller than expected among the offspring of parents with coronary disease. Changes in blood pressure and heart rate were not significantly different for these two small groups of subjects compared with those with normal parents, but levels of significance were approached in several instances. Accordingly, at present, cardiac output alone has been shown to have *both* important properties—that of giving satisfactory separation of subjects and of giving good correlation with family history. While the family history provides only indirect evidence of liability to future cardiovascular disease, it appears that, taken in conjunction with certain individual characteristics, it is helpful in pointing out susceptible persons.[4-6] From the above facts it appears that change in cardiac output after smoking is likely to be the most valuable part of the ballistocardiographic smoking test in screening possible candidates for hypertension or coronary disease.

In this paper, we have attempted to discover whether there are any factors which influence the response to smoking, since elimination of such sources of variation might "sharpen" the results. The only factor which seems important is the presence or absence of the fasting state which appears to change the magnitude of the response. This raises the question as to whether the tests performed before breakfast are measuring the same tendencies as those performed before lunch, that is, will the subjects tested before breakfast show a proportionate change if tested before lunch? In order to answer this question, we have calculated correlation coefficients between the results of the four sets of tests. Table XIX indicates that heart rate and cardiac output show good agreement.

TABLE XIX. CORRELATION COEFFICIENTS BETWEEN THE RESPONSES TO SMOKING (SERIES F)

MEASUREMENT	IA AND IB	IIA AND IIB	IA AND IIA	IB AND IIB
Systolic pressure	+0.202	+0.669***	+0.267	+0.500**
Diastolic pressure	+0.144	+0.641***	+0.242	+0.443*
Pulse pressure	−0.211	+0.225	−0.174	+0.178
Heart rate	+0.670***	+0.726***	+0.776***	+0.497**
Stroke volume	+0.158	−0.005	+0.050	+0.296
Cardiac output	+0.596***	+0.660***	+0.582***	+0.525**

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

This agreement is equally good whichever way the results are paired. Systolic and diastolic pressures show less satisfactory agreement. It seems legitimate then to conclude that the tests before breakfast and before lunch give similar information, but since the changes are on the average greater before breakfast, there is less danger that they will be obscured by experimental error. However, as shown in Table II, this increase in sensitivity has little practical effect on the

significance of the change after smoking, and there is little further difference between those done before lunch and those done at random (Table XVI). Accordingly, from our studies we conclude that there is little to be gained from fasting tests, and that tests performed at random times of day are satisfactory.

We have found few papers that deal with the quantitative aspects of the effect of smoking on the normal ballistocardiogram, and none which reported on the reproducibility of results.[7-9] Indeed, a search of the literature has shown that there is very little information on the reproducibility of the results obtained in repeated smoking tests of any type on the individual. The only reference which we have encountered is in a paper by Roth, in 1956, who writes, ". . . the increase in blood pressure and pulse rate during smoking varied little from day to day."[10] Unfortunately, she provides no figures or analysis of her results. In an earlier paper, however, the changes in blood pressure and heart rate after smoking are recorded for nine tests on one normal subject.[11] Calculation of standard deviations in this one case gave excellent agreement with the mean standard deviations in our Table X.

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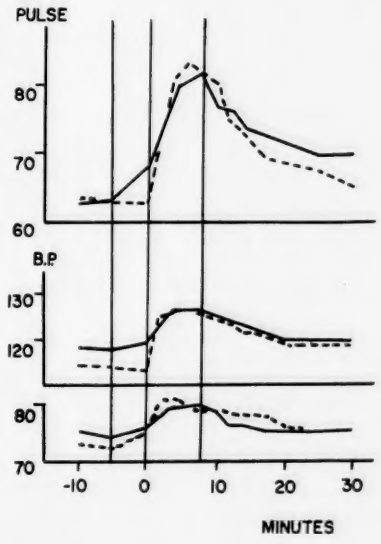

Fig. 4.—The influence of the fasting state on the circulatory response to smoking: average changes in 10 healthy subjects. From above down: pulse rate in beats per minute, systolic and diastolic pressure in mm. Hg. The broken line indicates the average of smoking tests performed in the fasting state, the solid line shows the average of tests in which a meal of pea soup immediately preceded smoking. The three vertical lines denote the times of beginning the meal (−5 minutes) starting to smoke (0 minutes) and finishing smoking (7½ minutes). It will be seen that in all measurements the value at 0 min. was lower when the subjects were fasting, but they showed a bigger rise on smoking and the "final" fasting figures (at 7½ minutes) were almost identical with the nonfasting values. (Modified from Ruosteenoja, R.: Effect of Food Intake on the Cardiovascular Response to Cigarette Smoking, Ann. Med. Exper. Fenn. **33**:320, 1955.)

Ruosteenoja compared the circulatory changes in 10 students aged 20 to 25 years (5 regular and 5 occasional smokers) under three sets of circumstances: immediately after a meal, on smoking after a meal, and on smoking after 15

hours' fasting.[12] In all other respects the test conditions were kept constant. These experiments show that there was a greater rise in skin temperature, systolic and diastolic pressure, and in pulse rate if the subject was fasting than there was after a meal (Fig. 4). In contrast to changes in skin temperature, which were highly significant, the differences in blood pressure and pulse rate were just significant at the 5 per cent level of probability. Although he makes no comment on the point, it appears from his diagrams, that the control values immediately before smoking were lower in the fasting state, and the highest figures after smoking were about the same whether or not the subjects were fasting. These data, therefore, agree nicely with our concept of the ceiling phenomenon which we have postulated as a result of the findings in Series F.

In a somewhat older group, Roth and Sheard found smaller differences in blood pressure and heart rate than we did when the changes on smoking in the fasting and nonfasting states were compared.[13] The discrepancies between their results and ours, however, do not seem great and may well result from differences in age and other characteristics of the subjects studied, as well as in the timing of the observations in relation to the last meal.

SUMMARY

1. A total of 245 ballistocardiographic smoking tests were done on healthy male medical students, all of them smokers. Sixty-nine subjects (Series O) had one test each at a random time in the day. To test the reproducibility of results 32 men had four tests each, two before breakfast and two before lunch (Series F) and 6 subjects had eight tests each under circumstances kept as standard as possible in every way (Series E).

2. The findings on a single smoking test in 113 students previously described, were essentially unchanged when the nonsmokers and female students were excluded, leaving the 69 subjects of Series O.

3. In 32 male smokers (Series F), smoking a cigarette before lunch produced results similar to those in Series O: a highly significant mean rise in systolic and diastolic pressure, heart rate, and cardiac output, and a fall in stroke volume. Pulse pressure was little affected. Compared with these tests, those performed before breakfast showed lower control readings, with a complementary increase in the response to smoking, so that the final figures after smoking were remarkably constant. Results were essentially the same on a second day. Heavier smokers tended to have lower control values and a bigger response to smoking. Exercise habits influenced the results little.

4. In the eight tests repeated on each of 6 subjects, the first test appeared to be an unbiased estimate of the mean. The reproducibility of the results was calculated, and it proved to be an individual characteristic, that is, mean confidence limits are of value in groups of subjects only. Analysis of variance shows that the change in systolic and diastolic pressures, heart rate, and cardiac output after smoking are likely to prove of value in classifying the subjects, but that for the other two measurements, the "overlap" of individual variation appears to be too great.

5. Comparison of the three series of tests revealed no great differences. The results in Series O, Series E, and the tests before lunch in Series F were substantially the same. The findings in Series F before breakfast were the only exceptions: in the main, control readings were lower and the response to smoking proportionately greater at that time than in any other series of tests. However, this enhancement of response seems of little practical value.

6. From these findings it appears that the ballistocardiographic smoking test, in which blood pressure, heart rate, stroke volume, and cardiac output are measured, gives results which are sufficiently reproducible for use as a screening test to classify young adults according to their patterns of circulatory reactivity. The results were materially unchanged by attempts to standardize further the test conditions, except that on the average, the response was more marked in the fasting state.

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CARDIAC EMPLOYMENT POTENTIAL IN URBAN SOCIETY

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IT IS generally recognized that there are some types of heart disease associated with the aging process. They are particularly prevalent from about the age of 30 years through the age of 65, the age group in which most persons are making their greatest social and economic contributions to society. Consequently, heart disease represents a major threat to a considerable proportion of our population and to the society as a whole through losses of talent, productivity income, and cultural contributions. There is, however, relatively little knowledge available on the extent to which heart disease represents an employment problem to either the employer or the employee. Such knowledge is needed in order both to implement action programs designed to aid the cardiac worker and allow society to realize their maximum potential. The American Heart Association, recognizing this need, has urged its state affiliates to gather such knowledge in their local areas.[1,2] This paper represents the results of a survey sponsored by the Minnesota Heart Association on the attitudes and practices of employers in the Minneapolis-St. Paul metropolitan area toward cardiac workers.

A primary objective of the survey was the determination of what attitudes and practices existed among Twin Cities' employers with regard to initial hiring of persons afflicted with cardiovascular diseases and also what policies existed with regard to individuals who had developed a heart condition during their employment. In addition to this, the data were analyzed to find out what, if any, significant differences in attitudes and practices were associated with the differential characteristics of various industries, e.g., whether they were engaged in manufacturing or wholesale activities, were large or small employers, had medical staffs attached, had an age policy requirement, or gave preplacement physical examinations.

METHOD USED IN THE STUDY

The entire study was contained geographically within the Twin Cities of Minneapolis and St. Paul. An initial sample of 100 Twin City employers, 67

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from Minneapolis and 33 from St. Paul, was selected using a stratified random sampling technique.*

In addition to the original sample of Twin Cities' employers, interviews were arranged with 10 large-scale business establishments at the request of the Minnesota Heart Association. The data for these 10 large-scale employers are presented separately from those of the larger sample in order to avoid limiting generalization from the original sample.

The basic technique used in the study was the directed interview. A schedule consisting of 29 items constructed in cooperation with members of the Minnesota Heart Association was used to gather the data.† The items pertained primarily to those behavioral areas which were considered to be possible problems of cardiac employment. The field work was carried out by two experienced interviewers. In almost all cases the subjects interviewed were persons directly concerned with and having authority to determine employment policies. In the case of the ten large-scale industries, top echelon management personnel were interviewed in each instance. In all cases, the interviewee was given complete assurance that neither his name nor the name of the business establishment would be connected with his responses.

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DESCRIPTION OF THE SAMPLE

The number of companies included in the final analysis was 99, of which 89 were from the random sample of Twin Cities firms. The other 10 business firms represent the specially selected group of large-scale establishments. Of the 89 firms, 17 were subsidiaries or branches of larger corporations, some of whom had main offices outside of the Twin City area and their policy regarding employment was sometimes determined by directions from the headquarters office.

In respect to the composition of the work force, that is, the distribution of male and female employees, the sample included 47 companies with less than 25 per cent female employees, 16 had 25 to 49 per cent female employees, 18 concerns had from 50 to 74 per cent female workers and 8 had over 75 per cent of their employees who were females.

The special group of 10 businesses was composed of 6 manufacturing firms, 3 service firms, and 1 retail firm. They varied in size from 500 employees to slightly more than 14,000 employees. Five of the firms employed 2,500 or more persons at the time they were interviewed.

PRESENTATION OF DATA

The data are presented in tabular form largely on the basis of type of business and size of establishment (number of employees). In all cases straight percentage distributions on items have been provided; in cases where the data ap-

*Due to noninterview of a number of establishments in the initial sample for such reasons as: (1) single proprietorships having no employees, (2) no longer in business, and (3) in one case refusal to cooperate, it was deemed advisable to make a re-draw of 22 additional establishments following the same method of sample selection used in the first case.

†Copies of the interview schedule used in this research are available for examination from the Minnesota Heart Association.

peared to warrant it, tests of significance of difference on the basis of differential characteristics of the businesses involved were made using the chi-square technique. The nature of the problem being investigated, as well as the nature of the data, did not justify more refined statistical treatment. Where only inadequate or insufficient data were available on an item and it was not tabulated, the reasons are given in the text of the report.

FINDINGS

Age Policy.—Slightly over one-third of the business firms interviewed reported having an upper age limit for employment. Only 8 of the 32 firms answering "yes" to this item indicated that such an upper limit was a formal policy. The upper limit varied from a low of age 30 years to a high of age 65 years. However as was often pointed out the specific age often depended upon the particular position for which the employee was applying. If, as often is the case in industry, the job to be filled required little training and remuneration was on an hourly basis, the upper age limit would not be as low as it would be in the case where the individual was hired with a view toward becoming a "key man" in the firm or for a particular position that required much skill and training at considerable cost to the company.

Often in the case where "yes" responses were received for age policy no specific limit was stated, especially in cases where the policy was an informal one. There were, however, a number of firms which cited what might be called an "age of hesitation," that is, the employer used this as a semi-fixed age level beyond which he would not go unless it was an unusual case where the talent or skill was such that it was necessary for him to employ beyond this point in order to obtain it. Furthermore, some employers indicated that labor market conditions played a significant role in their policies at any particular point in time.

There were, however, no statistically significant differences among the different types of firms on the factor of age policy. Only 5 of the manufacturing firms indicated they had an age policy, and of these 5 only 1 indicated that the policy was a formal one. In a number of the larger manufacturing firms the age policy, when it existed, was largely tied to the retirement pension plan provided for the employees. In most cases, if the employee was beyond 60 years old, it was felt that neither he nor the company would benefit from the program because of the age factor and, therefore, the company would not employ him (Table I).

The differences between the existence or absence of age policy were statistically significant when the firms were controlled on the basis of size. Only 20 out of the 69 firms with less than 100 employees indicated they had an age policy; on the other hand, 12 out of 20 of the firms with 100 or more employees indicated they had an age policy. On the basis of this it would appear that the presence of age policy in business is more a function of size than of business, the personnel problems consequent to such an increase in size require making policies explicit and to some degree formalized so that the various functionaries within the structure can carry out their functions in light of predetermined policy.

The policy regarding age limits was varied among the 10 establishments in the special sample. Three of these firms had a formal policy, 5 had an informal

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policy or age of hesitation for most types of employees, and 2 had no policy on age whatsoever. The age limits of these firms varied from a low of 40 to a high of 68. As was the case among the larger random sample, the upper age limits above 60 were largely determined by the nature of the retirement and pension program maintained by the particular company.

The youngest age limits were generally among the retail and service industries, while the older age limits were found most often in manufacturing and wholesale businesses. Many of those companies looking for persons primarily employed as sales personnel were holding their age limits between 30 and 35 for initial employment, particularly when the individual did not have previous experience. However, even if the individual did have experience, most of the firms hesitated to hire beyond the age of 40 years for sales purposes. A number of concerns were quite frank in stating that their past experience had been much better with younger, more flexible persons in their sales departments than with older persons and would continue to hire at the lower level.

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TABLE I. TYPE OF BUSINESS, NUMBER OF EMPLOYEES, AND POLICY REGARDING AGE LIMITS FOR EMPLOYMENT

TYPE OF BUSINESS AND NUMBER OF EMPLOYEES	POLICY REGARDING AGE LIMITS											
	UNDER 30	30–34.9	35–39.9	40–44.9	45–49.9	50–54.9	55–59.9	60–64.9	65–70	NO LIMIT	TOTAL NO.	PER CENT
Manufacturing												
less than 25										100.0	2	100
26 to 99		25.0						25.0		50.0	4	100
100 to 499						50.0				50.0	2	100
500 to 999											—	
1,000 or over					100.0							100
Wholesale												
less than 25					11.1					88.8	9	100
26 to 99										100.0	4	100
100 to 499				25.0					50.0	25.0	4	100
500 to 999											—	
1,000 or over											—	
Retail												
less than 25	3.3	3.3	6.6	3.3				3.3		80.0	30	100
26 to 99			20.0	20.0	20.0					40.0	5	100
100 to 499			50.0							50.0	2	100
500 to 999							100.0				1	100
1,000 and over									33.3	66.7	3	100
Service												
less than 25			12.5	12.5	12.5			12.5		50.0	8	100
26 to 99					20.0	20.0			20.0	40.0	5	100
100 to 499						16.7		16.7	16.7	50.0	6	100
500 to 999											—	
1,000 and over			100.0								1	100
Total	1	2	6	4	5	3	1	4	5	56	87	

If employment is, in part, a function of age in the larger firms and the age limit is tied to the requirements of a retirement policy (which in many cases requires a medical examination), it would appear that a cardiac's chances of

stable employment in large-scale industry might depend as much, if not more, on a fixed age of retirement than his cardiac condition.

Hiring of Persons With Cardiovascular Disease.—Of the 89 firms in the sample, 20 indicated that they did hire persons for initial employment who were known to be cardiacs. An unqualified "no" was given by 32 of the firms; and 37 of the firms indicated they would hire cardiacs "sometimes," depending upon the nature of the position to be filled. Although percentage differences do exist between the manufacturing, wholesale, retail, and service establishments on these responses, they are not statistically significant and cannot be relied upon to hold true for the universe of Twin City employers. The differences in percentages which exist on the factor of size and hiring also did not prove to be statistically significant.

It should be noted that when a "yes" response was given, a number of qualifications were usually given to the interviewer. In the case of the smaller-scale businesses it was clearly evident that a cardiac condition would make no difference in employment "provided the person could pull his own weight." In other words, most of the "yes's" were dependent upon the individual employee's cardiac condition not hindering work performance on the job. Considering the traditional stereotype of the inability of the cardiac to engage in active physical work (however false it may be), it is probable that a large percentage of these qualified "yes's" would behaviorally fall in the "no" category unless definitive information about the cardiac's ability to do the work was made available to the employer. This presents a real educational challenge to people in the area of heart research. Such information would not only ease the employer's decision-making but would also increase the social and economic security of the cardiac patient. In most of the cases those who responded to the item with, "sometimes, depending upon the nature of the job," would also tend to fall in the "no" category.

It appeared, from the comments of the various employers, that the "sometimes" response was largely dependent upon the needs of the business for a particular type of talent. If the nature of the cardiac's skill was such that it was scarce, then the "sometimes" would apply largely for the benefit of the business rather than any concern on the part of the business for the cardiac. In any event, it was quite clear that with regard to hiring, the employer did not feel obligated in any way to employ any individual whom he felt would in some way decrease the efficiency of his operations. Such a position is quite logical and consistent with the values governing efficiency of operations in business today (Table II).

These findings on the exclusion of workers with cardiac disease from new employment are supported by the results of a similar survey in Boston by Olshansky and his co-workers and by the nationwide survey of Lee and associates.[3]

Policies Toward Cardiacs and Other Disabled Workers.—On the question of policy regarding employment of cardiacs and the level of such policy, 38 firms indicated they had no policy of any type regarding cardiacs; on the other hand, 51 indicated they did have a policy. Ten of the firms that had a policy indicated it was on the formal level, and in 41 firms the policy was of an informal nature.

TABLE II. SIZE OF COMPANY AND HIRING OF PEOPLE WITH HEART DISEASE

NUMBER OF EMPLOYEES	EMPLOYMENT OF CARDIACS							
	N	% YES	N	% NO	N	% SOMETIMES	TOTAL N	PER CENT
0–9	11	36.7	8	26.7	11	36.7	30	100
10–19	4	25.0	5	31.3	7	43.8	16	100
20–49	2	14.3	7	50.0	5	35.7	14	100
50–99	2	22.2	3	33.3	4	44.4	9	100
100–249	—	—	5	50.0	5	50.0	10	100
250–499	1	25.0	2	50.0	1	25.0	4	100
500–999	—	—	1	100.0	—	—	1	100
1,000–2,499	—	—	1	25.0	3	75.0	4	100
2,500 and over	—	—	—	—	1	100.0	1	100
Total N	20		32		37		89	

While the firms did not differ significantly on the establishment of policy with respect to the factor of size, they did differ significantly on the basis of type of business. Without exception, the 9 manufacturing firms all indicated that they had an established policy regarding employment of cardiacs. Only 1 out of 18 of the wholesale firms had a formal policy, while 8 had a policy on the informal level. (Table III.)

TABLE III. KIND OF BUSINESS AND POLICY ON EMPLOYMENT OF CARDIACS

KIND OF BUSINESS	POLICY ON EMPLOYMENT OF CARDIACS							
	YES				NO		TOTAL	
	FORMAL		INFORMAL					
	N	PER CENT	N	PER CENT	N	PER CENT	N	PER CENT
Manufacturing	3	33.4	6	66.6	—	0.0	9	100
Wholesale	1	5.5	8	44.4	9	50.0	18	100
Retail	4	9.8	18	43.9	19	46.3	41	100
Service	2	9.5	9	42.8	10	47.5	21	100
Total	10		41		38		89	

In most cases the policy was simply one of either not hiring at all or only hiring on the recommendation of a physician for a specific position. That the behavior toward cardiacs was general to all types of disabled workers, and was not specific with regard to heart disease, was indicated by the response of 76 of the 89 firms. It was evident in the answers to these questions that most of the employers symphathized more with persons having an overt disability such as loss of sight, partial loss of hearing, or amputation of a limb more easily than

with the cardiac whose overt symptoms are not clearly noticeable. The interviewees often mentioned that it was extremely difficult to set any rigid criteria or exacting policy because of the lack of information on what a cardiac could or could not do. It appears that in those cases where there was a policy, it was in large part a result of extreme caution because of a lack of more adequate information on the work potential of various persons afflicted with cardiovascular ailments.

Very few of the firms made any effort to differentiate among the different types of heart ailments. Only 5 out of the 89 firms in the sample indicated any differentiation whatsoever, and this was not related to any particular characteristic of the different types of firms.

Among the 10 firms in the special sample, 7 indicated that they would not hire cardiacs, 2 firms indicated that they would, and 1 firm said hiring would depend entirely upon the nature of the position to be filled. Among these firms, 7 had a formal policy on hiring cardiacs, 2 an informal policy, and 1 had no policy at all. All 10 of the companies indicated that they viewed the cardiac as one among many types of disabled persons, and therefore their policy was general rather than specific to heart disease.

It is often assumed that a policy unfavorable to hiring of people with heart diseases would ordinarily be associated with a high percentage of males employed because of the greater prevalence of heart disease among adult males. However, the percentage of females employed by a firm made no significant difference in whether the firm did or did not hire people with a heart condition.

The major reason cited by the firms in this survey as a factor in their reluctance to hire cardiac workers involved their fear of increased financial costs if they were to hire cardiacs. This problem is discussed in more detail below.

Medical Staff.—Only one of the firms in the larger random sample maintained a full-time physician assisted by a part-time nurse. None of the firms that were interviewed had a full-time physician and nurse. Six of the firms had part-time physicians who were available varying from one morning per week to 3 days a week to consult on medical problems or give pre-employment physical examinations. Five of the firms in the sample were members of an industrial clinic to which they referred all of their medical problems including physical examinations. In total, only 16 firms out of the 89 in the sample had any type of medical service ranging from full-time physicians to a member of an industrial clinic or maintaining a part-time nurse. There was no significant difference with regard to cardiac employment policy between firms that had medical staffs or service of any type and those that did not have any medical staff or service whatsoever. In responding to the question of whether or not they would hire a cardiac, 3 of those firms with medical staffs indicated they would, 5 indicated they would not, and 8 indicated that they would hire depending upon the nature of the position involved.

In most instances, when a company had a specific blood pressure criterion for hiring workers, it was necessary to get in touch with either the medical director or the consulting physician. It was found that only 8 of the 89 companies had any specific blood pressure criteria by which they guided their employment prac-

tices. In most cases this ranged from 140 to 160 over 90 depending upon the age of the applicant. In a number of cases when the company physician was approached for the specific blood pressure criteria requirement, the usual explanation offered was that he did not believe that any specific criteria could be set up for employment, especially when one considers the number of factors that influence and condition the acceptance of any criteria of this nature. It appeared to the interviewers that on this particular item there was much doubt in the minds of even those persons who had given specific blood pressure criteria for employment as to their utility. It did not appear that they were taking the usual actuarial approach on this point such as they frequently did when rationalizing their position with regard to hiring cardiacs.

Only 2 of the 10 corporations in the special sample did not have any medical staff attached to them. A full-time physician and nurse were maintained by 4 of the corporations, and 2 of the corporations had a full-time nurse and a part-time physician. Of the other 2 large establishments, 1 had a full-time nurse and 1 was a member of an industrial clinic. Specific blood-pressure criteria were maintained by 5 of the 10 firms, and as was true for the larger sample, there was a general expression of doubt as to the utility of these criteria for employment purposes. A larger proportion of these firms, 4 out of 10, differentiated among types of heart disease than was true of the random sample. In most cases the differentiation was such that only minor cases could be employed, that is, the doubtful cases were usually resolved by not hiring the applicant.

Workers With Heart Disease.—Each company's representatives were asked whether they had in their employ at the time of interview any persons with high blood pressure, hypertension, or heart disease of any type. Of the 89 firms, 36 indicated they had persons in their employ who to their knowledge had some type of heart disease. There was, however, no statistically significant difference with regard to policy for initial employment of cardiacs and the presence or non-presence of cardiac workers in the corporation. Thus, it did not appear that incidence of employees with cardiovascular ailments was necessarily related to policy. In only a few cases was it possible to get any accurate count of the number of persons in these firms who had these disabilities, or what had happened to them after they had developed a cardiac ailment. Most firms did not keep adequate records on such cases and, consequently most of the data received were based upon the memory of the administrative officer being interviewed. In view of this, it was felt that the data were unreliable and any useful tabulation would not be possible. All of the special sample of 10 large businesses had persons with cardiac ailments in their employ at time of interview.

Policy Regarding Re-employment of Persons With Heart Disease.—A noticeable difference in the attitude of management personnel in all types of industry occurred when answering the question regarding re-employment of someone who had been afflicted with a heart ailment during his employment with the company. On the question of initial employment, the rationale regarding the cardiac was often in cold economic terms while on the question of re-employment a sense of moral obligation to the worker found strong expression among most interviewees. Only 4 of the 89 firms definitely said they would not continue to

employ an individual who was afflicted with a heart illness after he had been in their employ. These 4 firms used 2 rationalizations for this policy. The first was generally in terms of the benefit or welfare of the cardiac. The employer usually felt that his business was of such a nature that continued employment of the cardiac would be to his detriment and therefore would urge him to seek employment elsewhere. The second reason was given largely in terms of the economic factor; they usually classified their business as one which was highly competitive and in which any person afflicted with any illness whatsoever would not be able to hold up under the pressure and therefore would be a liability which the company could not afford.

In a number of cases the "re-hire in same job if possible" type of response had the emphasis on the "if possible." That is, the employer felt that it would be economically impossible to rehire the individual if he had a very severe attack which incapacitated him so that he would not be able to carry the major share of his previous work. This was particularly the case where the interviewee was a small business man with less than 10 employees. Also, in the smaller-scale businesses the opinion was expressed that the cardiac's fellow workers would be relied upon in large part to assume whatever duties the re-employed individual was incapable of fulfilling in order to minimize any excessive increase in cost of operation to the employer himself.

Several of the larger-scale businesses had persons in their employ, some of them disabled, who they felt contributed little or nothing to the general productivity, but it was the firm's obligation to maintain these persons until time of retirement or until an earlier retirement could be worked out for them. All 10 of the larger firms indicated that they would re-employ any personnel who had become afflicted after initial employment. The larger firms did, however, point out that their policy of not hiring cardiacs was in large part an attempt to avoid the occurrence of such situations.

Other factors which entered into their decisions and which tended to modify, in some respects, the re-employment policy were such things as: (1) the position of the person in the hierarchy, e.g., whether he was labor or management personnel and (2) the length of service with the corporation. The expression of moral obligation appeared to vary directly with the length of service. It was the interviewers' impression, however, that the moral obligation of the employer to the employee was much more intensely expressed in the case of the smaller-scale establishments than in the case of the large-scale firms. This, in all probability, is a result of the *personal* versus the *anonymous* relationship in small- and large-scale industry. It should be noted that the development of a cardiac ailment per se was not the reason for the moral concern of the management and would have been present in any case where the worker had become incapacitated for any reason whatsoever.

Of considerable importance to several employers in this survey was the factor of union seniority regulations. Seniority rules often were a complicating factor in attempting to provide a different type of job for an employee who had a heart attack. It is obvious that unions must become involved in any program attempting to place cardiac workers in industry. Perhaps the great interest of unions

in health plans will have some effect on modifying what at times appears to be a rigid attitude with regard to seniority problems.

Programs for Retraining Personnel and Referral to Rehabilitation Agencies.—None of the manufacturing firms in the random sample maintained any type of program for retraining persons with cardiac ailments or any other type of disability. Two each of the wholesale, retail, and service establishments indicated that they had a retraining program. The nature of this program was generally one in which all retraining was done on an individual basis. This was also true of the 10 larger establishments contained in the special sample. Five out of 10 of the companies in the special Minnesota Heart Association group indicated they had some type of provision for retraining, but none of them indicated that it was on a formal level. Employers felt that the infrequent number of cases of this type did not warrant the maintenance of a special program.

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Preplacement Physical Examination.—The frequency of preplacement physical examinations of any of the firms interviewed was very low. In the sample of 89 establishments only 12 required a preplacement examination. In the absence of a thorough preplacement physical examination a policy of not hiring cardiacs would appear to be relatively ineffective unless the applicant himself admitted the condition or it were known to the employer through other sources. A number of the firms did have the applicant fill out a medical history and as a partial substitute for a preplacement physical, asked the individual if he would be willing to take a physical examination. In cases where the individual refused an examination, the management then required a physical on the basis that the individual must have had some reason for refusing that might be detrimental to the company in the long run. If, on the other hand, the individual was willing to take the examination the companies appeared to be willing to take the risk in lieu of the expense connected with giving preplacement physicals.

Several of the companies interviewed had previously required physical examinations before hiring an applicant but felt that the cost (which most indicated averaged from twelve to fifteen dollars per employee) was not warranted on the basis of the rejections received. The interviewers were told that in most cases the rejections were less than ½ of 1 per cent. In one case, where the rejections for employment on the basis of physical examination ran 30 to 35 per cent, the director of personnel felt (1) that the requirements were too rigid for the nature of the work the employees were to undertake and (2) that the cost ran far beyond the savings to the company in the long run. A small group of companies which did not require examination upon initial employment did require an examination when the individual became eligible for the pension program. This, however, was not a requirement of the company so much as it was a requirement of the insuring firm and as such left the company in a position of disclaiming any obligation to the worker.

When classified according to type of business activity, there was no statistically significant difference among firms regarding the requirement of a preplacement physical examination. However, when classified according to size, firms employing less than 100 persons and firms employing over 100 persons, the difference was statistically significant; the data indicate that the requirement

of a physical examination is more a function of size than of type of business. In those cases where preplacement examinations were given they were for the most part given to all classifications of personnel rather than restricted to certain echelons. The fact that the physical examination is in part a function of size is further affirmed by the data for the establishments contained in the special sample, 9 of which required physical examination before employing the individual.

Increased Costs of Operation.—When queried as to whether or not the employment of cardiacs would increase their overhead or their cost of operation in any way, employers had not considered the situation enough in order to give any accurate estimate of how much or in what way the employment of cardiacs would tend to increase their cost of operation. The data on this item therefore tend to be "off-the-cuff" type responses of management personnel. A definite "yes" was given by 32 of the 89 corporations when asked if employment of cardiacs results in increased costs; 37 indicated a "no" response; and 20 indicated they didn't know whether it would result in increased costs. Of those who responded "yes" to this item, the two most frequent types of responses consisted of: (1) an increase in their industrial type insurance, and (2) a slow-down in productivity which would reflect itself in a higher cost per unit.

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Of the 10 firms in the special sample, 8 indicated that employment of cardiacs would definitely increase their cost of operation; one firm said it would make "no difference" largely because of the small frequency of such cases; and one firm indicated it "didn't know" whether it would increase their cost of operation as this data was not available to them. Several firms, each having several thousand employees and carrying their own insurance, believed their experience had indicated that hiring of persons with any disability would increase the cost to the corporation. Also, most of the larger firms had, at least in part, an assembly type of production and in such cases the productivity of any unit along the line is in large measure dependent upon other units along the assembly line. Thus if one person in the assembly line were unable to keep the pace, the effect would be felt throughout the productive process. Several firms pointed to the fact that persons affected with cardiovascular ailments were subject to sudden death; under such conditions the differential cost of a death on the job or a death off the job militated against the employment of cardiac workers.

The possible increase in cost of insurance and retirement programs was of considerable concern to the larger firms; on the other hand, it appeared that the productivity item was primary in the minds of the smaller concerns. That is, the relative concern of the small employer was minor in the matter of insurance since he felt that his rate was on an industry-wide basis and would not be appreciably affected by the employment of a cardiac. In most cases the remarks concerning possible increased costs were not specific to the cardiac but general to any disabled person. Even though a number of respondents had previously responded that they would hire cardiacs and also that they would rehire an individual if the ailment developed while he was employed by them, their response on the "increased costs of production" item was that if the individual did increase the cost of production, they had very little alternative except to replace

him. There were no statistically significant differences on the basis of type of size of industries regarding the factor of increased cost in production.

Results of this survey correspond to the findings of the Olshansky and Lee studies with respect to the deterrent of workmen's compensation costs and the costs of sickness and health insurance in the employment of persons with heart disease. Employers feel that the potential death and disability claims under existing workmen's compensation laws are a serious threat and consequently would rather avoid the problem by not hiring cardiacs. Part of this problem lies in the fact that the question as to whether cardiac disability and death may be caused by strain or trauma still appears to be controversial.[4] In at least one state, the strain or trauma aspect of employment in relation to a heart disease claim has been eliminated and "the cases are decided now purely upon the requirement that the injury occur in the course of the employment."[5]

Consultation With Work Assessment Clinic, Further Cooperation in Studies, and Willingness to Serve on Cardiac in Industry Committee.—Over 50 per cent of the respondents, 47 out of 87, indicated they would be willing to utilize a work assessment clinic if one were set up in the Twin Cities. Seven out of 9 of the manufacturing firms were interested in such a project, but only 18 out of 41 of the retail establishments thought they would have need for such a clinic. The employers generally thought that "anything that would improve the health" of their employees was a worth-while endeavor and they would be willing to participate in it. They felt that such a clinic would provide them with a more accurate evaluation of the cardiac's work potential, thus protecting them both from any possible difficulties arising out of the employment.

The most frequent condition placed upon the willingness of the companies to utilize a clinic was that the individual employee would be permitted to avail himself voluntarily of the clinic's facilities at the request of the corporation but would not be forced to utilize these services. Furthermore, since many of the business firms contacted were unionized, they indicated that such a policy would have to be cleared through the union officials and membership. The answers to a number of items in the schedule were frequently dependent upon the willingness of the union to have such a policy invoked. It would appear politic, therefore, before undertaking any program regarding cardiacs, that the full support of labor as well as management be obtained, for the success of any program appears to be dependent upon such cooperation.

When asked whether or not the firm would be willing to cooperate in further study of the extent of cardiacs among their personnel, 46 out of 89 among the larger sample indicated they would and 8 of the 10 firms in the special Minnesota Heart Association sample indicated they would be willing to cooperate in a further study.

The firms were generally willing to allow time but were skeptical about contributing funds to such a survey. Here again the employers emphasized that such a medical survey would be possible only if the employees and the union involved were willing to go along with such a program. It should also be remembered that notwithstanding the interviewer's emphasis upon frankness of replies, it was felt that a number of the "yes" responses were given largely in terms of

public relations. Whatever the reason for the "yes" response, be it public relations or a sincere desire to find out about cardiac ailments in industry, if they would permit such a study to be done, the same ends would be achieved.

Willingness to Serve on Committee.—In responding to the items regarding willingness to serve on a cardiac-in-industry committee for their own industry, most management personnel who responded affirmatively did so because they conceived of it largely in terms of a public service but not because of any deep interest in the subject. Even those individuals who appeared to be vitally interested, usually on a personal basis, in the problems of the cardiac shied away from committee membership. Only 27 out of the 89 indicated that they would serve on such a committee.

The Cardiac as an Employment Problem to Industry.—With one exception, and that largely on the grounds of the interviewee's involvement as a cardiac, the firms in the larger sample indicated that employment of the cardiac had never occurred to them as a problem and did not constitute a problem from the point of view of the employer although they fully realized that a problem may exist on the individual cardiac level. Those who did not regard it as a problem indicated that at the very most it constituted one of the minor difficulties faced in the general employment picture, insofar as the company was concerned.

Among the 10 larger firms in the special sample 4 of the 10 considered it a problem; but even in these cases it was pointed out that it constituted one of the less troublesome employment problems. It was conceived of as a problem by this group in a very restricted sense. Only when one of the high echelon persons had a cardiac condition would they consider it a problem.

It follows that if awareness constitutes a valid criterion of problem existence, those employers who felt they would have to be shown where the problem existed as far as the employer was concerned in logical terms were on sound ground. It would appear that if a problem does exist, it does not exist for the employers but rather for the individual cardiac seeking employment.[6] Thus, it would seem that the problem becomes one of determining what problems the cardiac faces, and secondly, in what manner can industry help to solve them. This also involves a task of convincing management that it should share in the solution of the problem of employment for the individual cardiac.

There is no easy solution to the problem of the cardiac worker. Many divergent groups have an interest in this problem, including physicians, employers, and unions, and these groups must come together and reach some basic agreements to improve the present situation. Compromise is clearly called for in areas of union seniority regulations, in changes in workmen's compensation laws, and in other areas of interest to help the worker with cardiac disease to obtain employment. Local heart associations can perhaps take leadership in bringing these divergent groups together to make some progress in dealing with this growing problem. More effort can probably be expended in educational efforts for employers to recognize that there are differences in employment potentiality of workers with different types of heart disease.

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EVALUATION OF AMPHETAMINE AS AN APPETITE DEPRESSANT

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PART I. CLINICAL

OBESITY presents a serious and common clinical problem, leads to increased morbidity and mortality, especially as related to the degenerative disorders, and results essentially from excessive caloric intake. The hazards of obesity have been discussed elsewhere, and there is unquestioned evidence of this relationship.[1-2] Excessive ingestion of calories resulting in derangement of the "intake/need" ratio is the common denominator and leads to increased fat deposition and weight gain, but the exact dynamics of this metabolic imbalance are not clear. Certainly endocrine, neuropsychiatric, metabolic and socioeconomic factors all pertain to the pathogenesis of obesity. This aspect has been recently reviewed by Parson and Crispell in their monograph on obesity.[3]

Obesity results only from a prolonged excess of caloric intake. Food energy which is assimilated in excess of the body's needs is stored as body fat. The corollary of this is that loss of body fat depends solely upon reducing the caloric intake below caloric utilization.[4] The recent increase in the investigation of obesity as the antecedent to decreased longevity, heart disease, diabetes, and arteriosclerosis, coupled with the renewed emphasis on the study of fat metabolism, points to considerable interest in this problem.

Since a relative excess of food intake appears to be the basic problem, a number of anorexogenic drugs have been developed and used, as an indirect approach to the clinical problem of obesity. The use of these agents is widespread because of the magnitude of the general problem. Amphetamine sulfate alone or in combination with dessicated thyroid is the most popular drug presently used for appetite control. The efficacy of this form of therapy has been reported by various observers. The mechanism of its action is not exactly determined, although it has been postulated that amphetamine has an effect on the cerebrum or on the hypothalamic centers.[5]

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A clinical study was undertaken using amphetamine, amphetamine and amobarbital, and amphetamine, amobarbital, and thyroid in combination, with all three preparations being dispensed in timed disintegration capsules.

Timed disintegration capsules are designed to provide in one capsule the equivalent of three individual doses of the medicament; approximately one-third of the total dosage is released initially, and the remaining two-thirds of the dosage is released uniformly over a period of 6 to 8 hours, providing an effect for 10 to 12 hours.

Thirty-five obese patients, 3 men and 32 women, were included in the study and were seen weekly or biweekly for a 2-month period. These patients were referred from the general medical clinic for treatment of their obesity. Those with suspected endocrine disorders and patients with concomitant serious vascular, cardiac, or infectious disease were excluded. History, physical examination, and laboratory studies (including hemoglobin, hematocrit, white cell count, urinalysis, and fasting blood sugar) were completed prior to beginning treatment. In certain instances, when it was indicated, electrocardiograms or chest films were taken.

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All patients included in the study were obese and, in most instances, obesity was a singular problem. Two patients were followed in preparation for cholecystectomy necessitated by cholecystolithiasis and chronic cholecystitis. A small number were referred by the orthopedic consultants for weight reduction because of orthopedic disease aggravated by obesity.

All treatments were administered in one daily dose, in timed disintegration capsules 30 minutes before breakfast. The different combinations of medications were administered at random to patients except to the group given the combination including thyroid. This was arbitrarily limited to the younger patients only. Discrepancies in the total number of patients in each group are related to losses due to inadequate follow-up and limitation of the thyroid to younger individuals.

Methods and Results.—The medications* used in this study were as follows:

Group I (13 patients)	
d-Amphetamine sulfate	15 mg.
Group II (16 patients)	
d-Amphetamine sulfate	15 mg.
Amobarbital	60 mg.
Group III (6 patients)	
d-Amphetamine sulfate	15 mg.
Thyroid	195 mg.
Atropine sulfate	0.35 mg.
Aloin	16 mg.
Phenobarbital	16 mg.

*Manufactured by Victor M. Hermelin and Company, New Products Division K-V Pharmacal Company, St. Louis 17, Missouri.

Patients were cautioned regarding the side effects of amphetamine, asked to record any undue nervousness and note degree and time of onset. In addition, instructions were given to discontinue the medication if symptoms were severe or persistent. No specific dietary instructions were given, initially. If, after a period of one month, caloric intake had not decreased as judged by reduction of body weight, specific dietary instructions were given and weight-reducing diet lists supplied. Each patient was seen weekly or biweekly for 8 weeks, and on each visit blood pressure, pulse, and weight were noted and recorded.

The hemogram and urine of each was checked again either midway or at completion of the 8-week period. Questions pertaining to anorexia, anxiousness, nervousness, insomnia and dizziness, or other manifestations of toxicity were asked, and an effort was made to define the degree of these subjective findings. A single observer conducted the entire study and saw each patient on each of his or her clinic visits.

The total incidence of subjective reaction to the various drugs and combinations is summarized in Table I.

TABLE I. SUBJECTIVE REACTIONS TO AMPHETAMINE

	GROUP I (13 PATIENTS)	GROUP II (16 PATIENTS)	GROUP III (6 PATIENTS)
Symptoms			
Anorexia	10	7	6
Nervousness			
Mild	3	3	0
Moderate	2	0	0
Marked	1	0	0
Insomnia	1	2	0
Dizziness	1	1	0

TABLE II. ANOREXIGENIC EFFECT (35 CASES)

	SECOND WEEK	FOURTH WEEK	SIXTH WEEK	EIGHTH WEEK
Mild	14	5	4	6
Moderate	8	8	8	4
Marked	1	1	0	0
Total	23	14	12	10

In regard to amphetamine-induced anorexia, two features were noted. Approximately two-thirds of all patients initially had some indication of the anorexigenic effect. This effect was sustained in only 12 patients. In addition there was a tendency in the patients with more prolonged anorexia to show decrease of anorexia during the second month as tolerance apparently developed. This has been noted previously.[5] A summary of these data can be seen in Table II.

Fig. 1 represents a comparison of the weight loss curves of the three individual groups. The curves are plotted on the basis of percentage of initial body weight. As can be seen, the curves are essentially parallel, and there is no significant difference between the group given amphetamine alone, the group given amphetamine and amobarbital, and the group given amphetamine, thyroid, and phenobarbital. Initially the latter group lost slightly more weight, but this advantage was not sustained. Group III has the smallest number of patients, but it appears that thyroid added little to the efficacy of amphetamine.

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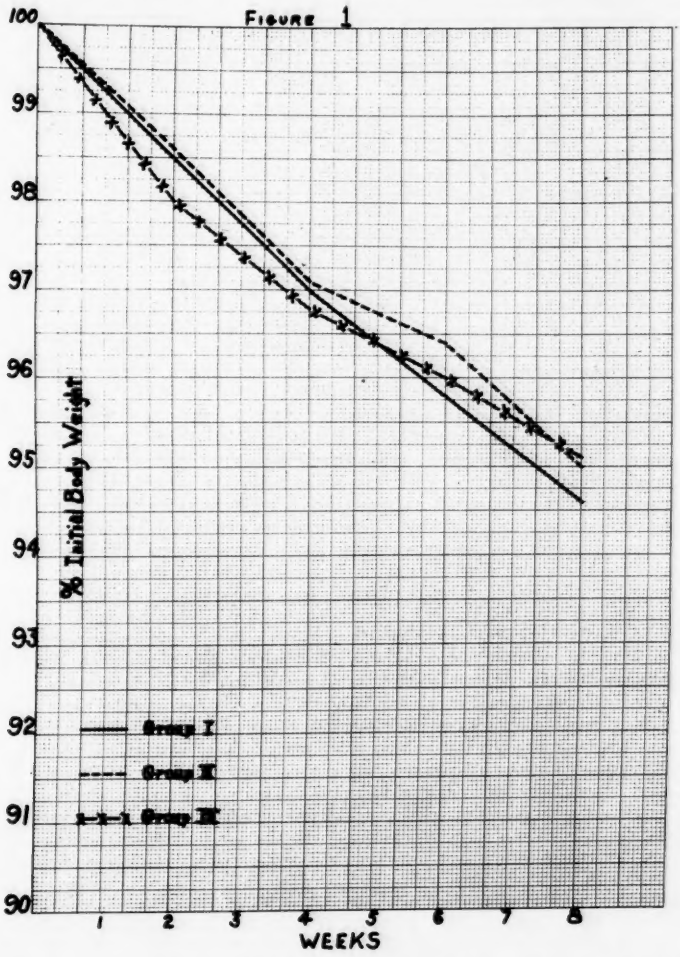

Fig. 1.—Weight loss curves of Group I (amphetamine), Group II (amphetamine and amobarbital), and Group III (amphetamine and thyroid).

Fig. 2 compares the weight reduction of (a) the total group (35 patients), (b) the group of 8 patients noted in Tables I and II as having had sustained,*

*At least 6 weeks.

moderate, or marked anorexia, and (c) the other patients. As can be seen, the weight loss is greater and averages approximately 1 per cent per week in the symptomatic group. It can be seen that those patients who remained relatively free of anorexia have a more gradual decline in weight. The efficacy of amphetamine as an adjunct in treatment of obesity appears proportional to the degree of anorexia induced, and a moderate sustained degree is probably necessary if the com-

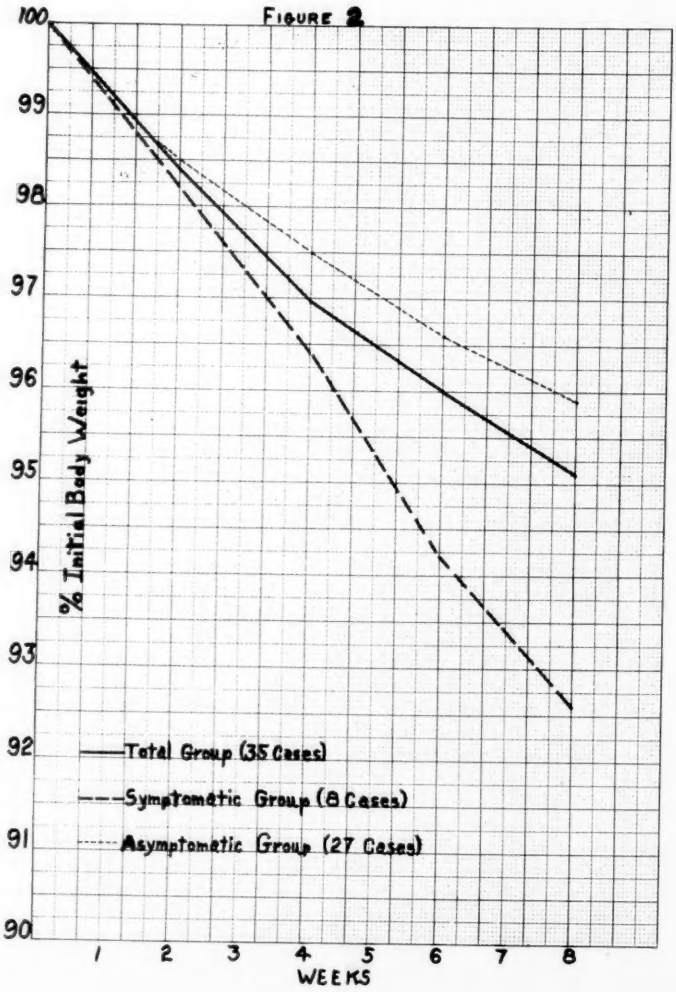

Fig. 2.—Weight loss curves of total group, symptomatic group, and asymptomatic group.

pound is to produce significant effect. Because of the onset of early tolerance in certain patients and the danger of habituation in others, amphetamine should be used only for a limited time during the initial phase of re-adjustment in the obese patient. The addition of amobarbital to amphetamine in the dosage used

in this study seemed to have little effect on incidence of side effects or change in weight loss. Larger doses of amobarbital may reduce objective symptoms but also might detract from the therapeutic effect.

PART II. LABORATORY

Timed disintegration preparations are designed to make a sufficient amount of the drug immediately available to produce the desired therapeutic effect and to make the remainder of the drug available at a rate which will maintain therapeutic activity for an additional period. In vitro tests are designed for manufacturing control purposes only and do not necessarily reflect the action of the drug in vivo. Each timed disintegration medication must be individually constructed according to the physical and biologic properties of the drug.[6]

Butler, Mahaffee, and Waddell[7] have published work on blood levels of phenobarbital in tablets and timed disintegrating capsules. Roentgenographic studies by Feinblatt and Ferguson[8] have established that a drug in timed disintegration capsules is released at certain intervals in the gastrointestinal tract. Subsequently, these authors have published work[9] correlating subjective observations and x-ray studies.

Methods and Results.—An adaptation of the method for the determination of antihistamine blood levels by Porter and Silber[10] was utilized for determining amphetamine blood levels. The method is based on the ability of certain drugs to form soluble compounds with various dyes in organic phases. A sample of blood serum to be tested for amphetamine content is combined with a buffer solution of brom thymol blue and extracted with ethylene dichloride. Amphetamine combines with the dye quantitatively and after further extraction from the organic phase by an aqueous solution of sodium hydroxide, the color intensity is read on a spectrophotometer at wave lengths of 580 mμ and 620 mμ.

The buffer solution (pH 5.3) is prepared by dissolving 19.0 Gm. monobasic sodium phosphate and 1 Gm. anhydrous sodium phosphate in water and then diluting to 500 ml. The dye solution is prepared by dissolving 0.2 Gm. brom thymol blue in 15 ml. of water and 3.2 ml. of 0.1 N sodium hydroxide made up to 250 ml. with water.

Standards are prepared by adding graduated amounts of amphetamine to blood serum and a calibration curve is made from the reading of each sample at wave lengths of 580 mμ and 620 mμ. Zero optical density of the spectrophotometer is determined on a blank solution of the buffer and dye solutions. Two milliliters of the serum to be treated are used for each determination, and results are reported in milligrams of amphetamine per milliliter of serum.

Ten normal, healthy subjects (male medical students in the age group of 20 to 25 years) were selected. Each subject was given a 15 mg. d-amphetamine timed disintegrating capsule 30 minutes before breakfast and a blood sample of 15 ml. drawn immediately. The subject then ate a normal breakfast and blood samples were drawn at 2-, 4-, 6-, 8-, and 10-hour intervals. Results are reported in Table III. Fasting specimens showed less than 0.005 mg. amphetamine per milliliter of serum, which is insignificant and within the limits of experimental error of the method. These data (Table III) indicate that amphetamine is absorbed

slowly into the blood stream and that there is obviously considerable variation among individuals, both as to rate of absorption and the total amount absorbed. However, it is evident that the medication in timed disintegrating form is fairly uniformly absorbed after the first 2 hours (Fig. 3.). Only 2 of the group of 10 subjects reported any degree of excitation or nervousness, and this was only temporary, about the sixth hour of the experimental period.

Fig. 3.—Average amphetamine blood levels, TD capsules; 10 cases.

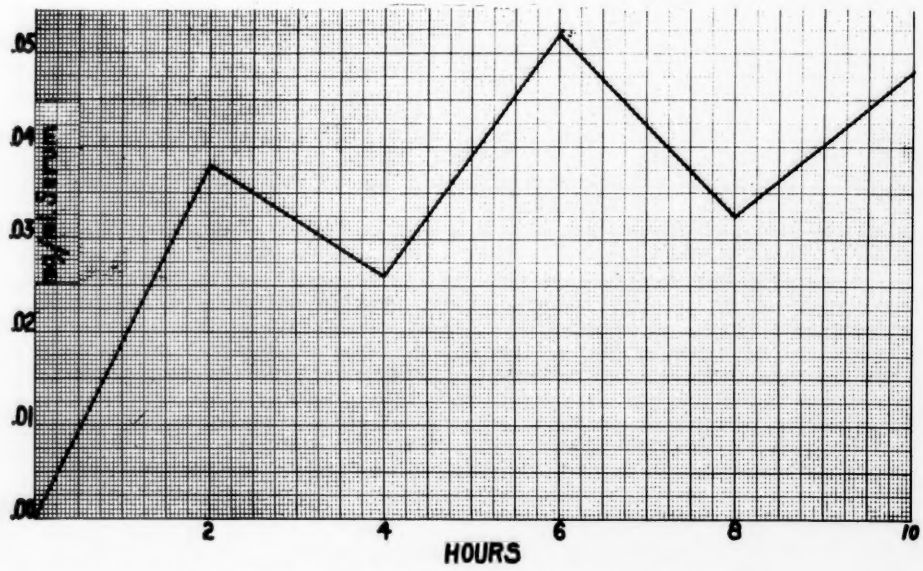

Fig. 4.—Average amphetamine blood levels, 5.0 mg. tablets t.i.d.; 5 cases.

For comparison purposes, 5 subjects from a similar group of medical students were given 5 mg. d-amphetamine sulfate tablets at 7:00 A.M., 10:00 A.M., and 2:00 P.M. Blood specimens were drawn at 7:00 A.M., 9:00 A.M., 11:00 A.M., 1:00 P.M., 3:00 P.M., and 5:00 P.M. Results are reported in Table IV. Obviously, there is a rise and fall in blood serum levels of amphetamine following each dose (Fig. 4). Each of the subjects in this group reported some excitation and nervousness at the sixth and tenth hours. These side effects were more evident than when similar subjects received the same amount of d-amphetamine sulfate in one timed disintegrating capsule.

TABLE III. AMPHETAMINE 15 MG. TD CAPSULES (10 CASES)

	HOURS				
SUBJECT	2	4	6	8	10
A	.034	.040	.050	.048	.045
B	.030	.036	.045	.040	.035
C	.025	.028	.032	.035	.030
D	.028	.029	.035	.029	.035
E	.042	.045	.042	.038	.038
F	.030	.036	.040	.030	.028
G	.032	.034	.038	.040	.030
H	.022	.028	.042	.030	.045
I	.020	.022	.040	.050	.040
J	.020	.020	.039	.049	.055
Average mg./ml.	.028	.034	.042	.041	.038
Maximum mg./ml.	.042	.045	.050	.050	.055
Minimum mg./ml.	.020	.020	.032	.029	.028

TABLE IV. AMPHETAMINE TABLETS (5 MG. × 3)

	HOURS				
SUBJECT	2	4	6	8	10
K	.045	.033	.065	.038	.050
L	.035	.028	.043	.032	.040
M	.034	.024	.050	.025	.038
N	.036	.022	.060	.033	.065
O	.038	.020	.052	.035	.045
Average mg./ml.	.038	.025	.054	.033	.047
Maximum mg./ml.	.045	.033	.065	.038	.065
Minimum mg./ml.	.034	.020	.043	.025	.038

CONCLUSIONS

1. Fifteen milligrams of d-amphetamine sulfate in timed disintegration (TD) capsule form is temporarily effective in suppressing the appetite, with weight loss being proportional to the degree of anorexia.

2. Sixty milligrams of amobarbital combined with 15 mg. of d-amphetamine does not appear to add to the effectiveness of amphetamine in suppressing the appetite and does not alter the incidence of hyperirritability, nervousness, and insomnia.

3. Thyroid did not appear to augment the value of amphetamine in depressing the appetite and increasing weight loss in a small group of patients.

4. Blood level studies confirm the gradual sustained absorption of amphetamine in TD capsules.

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Review

PSYCHOTOMIMETIC DRUGS

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PART I: BACKGROUND

FOREWORD

MODERN interest in the psychotomimetic drugs goes back more than a hundred years[79] and active experimentation more than 75 years.[64,101] In this time a vast literature has accumulated. It is not the intention of the reviewer to attempt to describe all of this. It is important, then, that present purposes be explicitly stated: (a) to cover originally observed facts and statements of concepts; (b) to present current views concerning the effects, the uses, the difficulties, and the possibilities inherent in the psychotomimetic drugs, especially as they have been studied in man; (c) in all of this, to emphasize the well-designed study when encountered—and what seem to be the requirements for such study—and to give suitable emphasis to *quantitative* data wherever it can be found. The reviewer holds with Lord Kelvin that ". . . when you can measure what you are speaking about, and express it in numbers, you know something about it . . . when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of *Science* . . . ." A final purpose is to arrive at some general conclusions concerning work in this field.

THE AGENTS

Moreau in his monograph *Du hachisch et de l'aliénation mentale* wrote in 1845: "By its mode of action on the mental faculties, hashish gives to him who submits himself to its strange influence the power of studying, on himself, the moral disorders which characterize mental illness, or at least the principal intellectual modifications which are the points of origin of all kinds of mental disturbances." Perhaps he was influenced by Davy[22] and by De Quincey,[25] and Moreau may have stimulated Benjamin Paul Blood's interest in the "Anaesthetic Revelation."[13] This latter work excited William James's interest[57] in the field. These matters have been discussed by Beecher.[7]

For some years there has been widespread interest in the possibility that schizophrenia might be explained on a chemical basis. The beginnings of this modern interest go back to specific experimental work begun 75 years ago. Kraepelin[64] worked on the psychic effects of drugs and this was followed by Schmiedeberg's production[101] of cataleptic phenomena in rabbits and pigeons (but not dogs) with ethyl-urethane. Heffter observed the peculiar effects of mescaline on dogs. A great impetus has been given to work in this direction by studies of mescaline effects over the past 20 years.[42,111] And more recently, study of lysergic acid derivatives has received a great deal of attention (Stoll and Hofmann,[112,114] Stoll,[115-117] Hoch,[52] Hoch, Pennes, and Cattell,[53] Mayer-Gross,[76] Rinkel, DeShon, Hyde, and Solomon,[90] Elkes, Elkes, and Bradley,[28] von Felsinger, Lasagna, and Beecher,[121] Purpura,[86,87] Evarts,[30] Hoagland,[48] Osmond,[81] Osmond and Smythies,[82] Rothlin[95]). In general terms the recent interest in correlating biochemical changes and schizophrenia arises in part, for example, from the demonstration of a relationship between phenylketonuria and mental aberration, in such similarities as exist between mental disease and drug-induced psychoses and, not least, the modern possibilities for measuring minute quantities not only of drugs but also of naturally occurring substances in the body.

While the amount of quantitative data on the effects of drugs in this area is at present meager, it will doubtless increase rapidly in volume and in importance. For these reasons, a fairly extensive background is presented for such quantitative data as are available. This background is described in some detail because it is evident that many effects of the psychotomimetic drugs will lend themselves to quantitative study. Such quantitative values, when established, may mark differences, not now apparent, among the many agents. Such material may also afford insight and avenues of approach not only into differences among the drugs but also, when the drug effects are compared with the signs and symptoms of mental disease, into certain aspects of the nature of such disease. The importance of this area and the possibilities in it, rather than the amount of useful quantitative data now available are reasons enough for discussion.

This new class of agents has received many labels, called variously phrenotropic, psychotogenic, schizophrenogenic, psychehormic, psycherhexic, psychezymic, psychelytic, or psychedelic agents, hallucinogens, schizogens, psychotogens, psychotica, phantastica, or elixirs. A partial list of drugs said to produce psychotic reactions is as follows (Hoch, Pennes, and Cattell)[53]: acetanilid, acetylsalicylic acid, adrenochrome, adrenolutin, alcohol, amphetamine, arsenic, Atabrine, atropine, barbiturates, bromides, bufotenin, caffeine, chloral hydrate, cocaine, diisopropyl fluoro-phosphate (DFP), ergot alkaloids, hormones (various), lead, lysergic acid (both di- and mono-ethyl amides), mercury, mescaline, N-allyl-normorphine, quinine, scopolamine, tetraethylpyrophosphate (TEPP), water (toxic amounts). This is, to say the least, a heterogeneous group of compounds. Here, as always, the difficult problem arises of eliciting a relationship between chemical constitution and pharmacologic effect.[76] This is baffling to the point of impossibility at present. A very wide variety of chemical compounds seems to produce the same or very similar effect. The stakes are high and the challenge great to uncover relationships between structure and psychic effect.

It is believed that these agents on being administered to normal individuals can mimic certain forms of mental disease. Certainly they can produce great subjective change. As Hoagland[48] puts it, "Psychotomimetic drugs are tools capable of producing brief and controllable experimental psychoses in normal persons, and they thus open new channels for the investigator." Just how precise the mimicry of psychotic states is is not yet clear. This capacity may not even be their most important action.[81] Osmond[81] has sought a definition of such agents which leaves out those acting in large part on the body (as well as on the mind). In his definition he wishes to exclude anesthetics, analgesics, hypnotics, alcohol and the derivatives of atropine and cocaine. He suggests, "Psychotomimetic agents are substances that produce changes in thought, perception, mood and sometimes posture, occurring alone or in concert, without causing either major disturbances of the autonomic nervous system or addictive craving, and although, with overdosage, disorientation, memory disturbance, stupor and even narcosis may occur, these reactions are not characteristic." Evarts[30] requires that the psychotomimetic substances produce a psychosis in a high proportion of the subjects who receive them.

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It must be emphasized that although our interest in these agents is a limited one, the psychotomimetic agents produce profound subjective change and insofar as this has been dealt with in a quantitative way it is pertinent to the theme of this review. While the quantitative work done to the present time is, as mentioned, meager, unquestionably it will grow rapidly. It will likely arise from the following background.

BRIEF HISTORICAL NOTE

There is nothing new in man's attempt to alter the workings of his own mind. This is as ancient as the history of the human race and doubtless antedates history. Osmond*[81] takes a very long look into the past. He starts with:

> ". . . the still-unidentified soma imported from central Asia into India several thousand years ago and ending with 3,4,5,trimethoxyphenyl-β-aminopropane (TMA), bufotenin, adrenochrome, and adrenolutin whose qualifications for inclusion in this classification are still being examined. As I list these treasures of 5000 years of perilous and sometimes fatal searching, think upon those nameless discoverers and rediscoverers, Aztec and Assassin, Carib and Beserker, Siberian and Red Indian, Brahmin and African, and many others of whose endeavors even scholars do not know. We inherit their secrets and profit by their curiosity, their courage, and even from their errors and excesses. Let us honor them. They do not appear in any list of references.
>
> "There are such substances as soma, hashish, cohoba, ololiuqui, peyote, the Syrian rue, the caapi vine, the fungus teonanacatl, the two Amanitas, pantherina and muscaria, the iboga bean, and the fierce virola snuff obtained from a nutmeglike tree in Amazonia. Who knows what other compounds await the keen inquiries of ethnobotanists such as R. E. Schultes or mycologists such as Gordon Wasson?

*I should like to acknowledge my indebtedness to the interesting review of Osmond for guidance in historical matters.

> "With our modern synthetics we are a little safer, though the ground quakes beneath us. These synthetics include mescaline, introduced by Heffter in 1896, the first, I believe, of these agents to be synthesized; harmine or telepathine, an alluring name whose significance I have never understood; Hofmann's astonishing lysergic acid diethylamide (LSD), whose great activity has made homeopathy seem less improbable; hashish, whose still-uncertain active principles should surely be ascertained; TMA, synthesized by Scott and his co-workers of Imperial Chemicals Ltd., Manchester, England, a synthetic that lies in an area intermediate between mescaline and amphetamine and has recently been the subject of a report by J. R. Smythies; bufotenin, isolated from cohoba, a West Indian snuff; unstable adrenochrome; and the subtle adrenolutin. What an array of substances for daring inquiry! What work for generations to come!"

Recent interest in this field has become very great and many facets of this problem are being attacked in a fairly orderly and sometimes scientific way.

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AREAS WHERE PSYCHOTOMIMETIC AGENTS ARE OF INTEREST

The "Model Psychoses."—More than a hundred years ago[79,81] hashish was used to give students of mental disease insight, it was hoped, into what the mentally ill endured. Work in this area has been stimulated in recent years by studies of the effects of mescaline. Osmond[81] credits Schueler[102] with being the "founder of model therapies" in 1934. See the fairly recent work of Stockings,[111] Mayer-Gross,[76] and Hoch.[52] But above all the extraordinary effects of the diethylamide of lysergic acid, the so-called LSD, has aroused interest here, following its introduction by A. Stoll and Hofmann[113] and study by Stoll.[115,117] The papers of Osmond and Smythies,[82] Rinkel, Hyde, and Solomon,[91] and Anderson and Rawnsley[3] should be consulted.

Osmond[81] speaks regretfully of his uncertainty as to whether the psychotomimetic agents mentioned above differ quantitatively or qualitatively, since no studies have "taken into account obvious variables such as body type, height and weight, or skin and eye color, let alone subtle personality or cultural, social, and biochemical factors that may be very important." Important as most of these factors doubtless will be shown to be in the future in determining the effects of drugs that alter subjective responses, the writer knows of no single drug, old or new, which can be said to have been adequately studied from all these points of view. A long-standing interest of Beecher's laboratory has been to devise techniques for correlating, if possible, personality type, for example, with drug action. In some years of work an encouraging mass of data has been accumulated, but only a tentative beginning has been published.[8,9,41,68,108,120] It is true that most of these variables must be taken into account if drugs that alter subjective responses are to be evaluated soundly and understood.

Discussion of the relationship of model psychoses to schizophrenia is at least 50 years old.[81] The work of Osmond and Smythies[82] aided greatly in clarifying the difference between the two. Osmond[81] refers to his work with his associates on ololiuqui, adrenochrome, and adrenolution.

Eventually, model psychoses induced with drugs[81] must be related to those produced by other means such as the specialized "isolated" environments of Heron, Bexton, and Hebb[45] and Lilly.[69]

Psychotherapy With the Psychotomimetic Drugs.—In considering pharmacotherapy in psychiatry Margolis[72] says: "Although chlorpromazine and reserpine have been depicted as highly effective therapeutic agents by a legion of investigators, considerable disagreement still exists as to the actual value of these drugs. They have been considered by some as worthless, or as having only a sedative action, and as having no effect beyond the period of administration. In other quarters they have been regarded as superior to electroconvulsive and insulin-coma therapy and even as 'curative' in nature. They have been described as both a valuable adjunct and as a hindrance to psychotherapy."

Margolis's review provides an abundance of evidence of the confused situation just described: Too many have approached the most complex field of therapy with very nearly complete disregard for the controls that are essential to sound conclusion.

Among the many claims and counterclaims regarding the psychotomimetic agents, it seems to be widely agreed that both physical and psychologic effects of lysergic acid diethylamide are less in schizophrenics than they are in normal individuals. Schizophrenic patients are quite resistant to effects from ordinary doses of lysergic acid diethylamide.[11,21,39,48,100,105]

Osmond[81] and others (following Moreau[79]) maintain that self-administration of these agents is "the essential precondition for such work," that only in this way can an adequate understanding of what these agents are capable of be attained. Several recent studies report the use of these agents in therapy (Sandison,[99] Abramson,[1] Frederking,[33] Busch and Johnson,[17] Anderson and Rawnsley,[3] Osmond[81]).

Part II: Effects

Biochemical Studies

While very little data are at present available on the distribution of the psychotomimetic substances in the body, an excellent start in quantitative terms has been made. Such quantitative work is essential if work on the model psychosis is to be placed on a dependable basis. See, for example, the studies by Axelrod, Brady, Witkop, and Evarts.[5] This work in monkeys indicates that while the lysergic acid diethylamide leaves the plasma rather rapidly following intravenous injection, about half being gone in 100 minutes, this disappearance is presumably due largely to a shift of the drug from the plasma to the tissues. The drug is found (by chemical means) in decreasing order of concentration in bile, plasma, lung, liver, kidney, brain, intestines, spleen, cerebrospinal fluid, muscle, and fat. Lysergic acid diethylamide, according to these investigators, is almost completely metabolized in the body (in monkeys, cats, mice) with only negligible amounts excreted in the urine and stools. The in vitro metabolism of lysergic

acid diethylamide is "markedly" inhibited by chlorpromazine and "moderately" by serotonin.

Hoagland[46] on studying C^{14}-labeled lysergic acid diethylamide in rats found 30 minutes after injection the following percentages of theoretically equal distribution of counts: liver 135, cortex 31, thalamus 28, cerebellum 26, brainstem 17, hypothalamus 16. Further distribution data from other investigators are reported by Hoagland.[48]

There is a growing belief, in some quarters at least, that schizophrenia is to be explained on "chemical" basis. The spur given to study of drug-induced psychoses by the discovery of lysergic acid's effects has led to an increased interest in the biochemical derangements produced by the psychotomimetic drugs and to a comparison of these observations with those found in schizophrenia. These matters have recently been reviewed by Hoagland[48] and cannot be considered in detail here. He and his associates have observed similarity between schizophrenic patients and normal subjects treated with lysergic acid, in adrenocortical function and excretion of phosphate. This group has considered the possibility that this supports the hypothesis of a biochemical factor in the cause of schizophrenia (Hoagland, Feldstein, and Dibner,[50] Hoagland,[46] Bergen and Beisaw,[12] Hoagland, Rinkel, and Hyde,[51] Hoagland and Bergen,[49] Slocombe, Hoagland, and Tozian,[107] and Slocombe.[106]). It is important that techniques for appraising the relative merits of these agents be developed and applied.

The careful review of Koelle on the pharmacology of mescaline and d-lysergic acid diethylamide may be consulted for material relevant to this section but which for reasons of space cannot be included here. His review of laboratory studies is especially useful in augmenting and supplementing the present account.

NEUROPHYSIOLOGIC EFFECTS

Effects of Psychotomimetic Substances on Synaptic Transmission.—(Evarts[30])

Lysergic acid diethylamide: Little work in this area has been done in man, for obvious reasons, and animal work must be consulted. Marrazzi and Hart[74,75] have studied in anesthetized cats the cortical response to stimulation of the contralateral cerebral hemisphere. Lysergic acid diethylamide reduced the amplitude of the postsynaptic component of the transcallosal response. Purpura,[85-87] with unanesthetized cats, found that lysergic acid diethylamide caused facilitation of the primary cortical responses to a click as well as to light stimulation. In his study the cats were immobilized with succinylcholine. Lysergic acid diethylamide also produced changes in the recovery cycles in these two systems. Rovetta[96] with a very large dose of lysergic acid diethylamide (40 mcg./kg.) failed to find in anesthetized cats any clear effect on the cortical responses to photic stimulation. In cats anesthetized with pentobarbital sodium, Evarts, Landau, Freygang, and Marshall[31] in studying the effect of lysergic acid diethylamide on synaptic transmission in the visual system of the cat found an average decrease of 80 per cent in the amplitude of the postsynaptic geniculate response to a single shock to the optic nerve. "Whereas geniculate transmission was blocked by LSD, transmission within the retina and between geniculate radiation fibers and cortical

cells was extremely resistant to inhibition by LSD." There are great differences in the effects of lysergic acid diethylamide on various synapses.[30] Evarts found that pentobarbital sodium sensitized (in comparison with curarized animals) his preparations to the action of lysergic acid diethylamide. This may explain the difference between his work and that of his associates referred to above, and that of Killam and Killam.[59] The latter group used curarized but not anesthetized cats and found that even large doses of lysergic acid diethylamide (up to 100 mcg./kg.) did not alter the thalamic recovery cycle following peripheral stimulation of mixed nerves, nor was the amplitude of the recorded electrical activity changed. The difference might also be due to the fact that the two groups studied different sensory pathways.

Lysergic acid diethylamide blocks the effects of serotonin on the flexion reflex of the cat.[104] The vascular effects of serotonin might possibly have played a role in this result. These must be ruled out.[30]

Mescaline: This agent inhibits the postsynaptic component of the transcallosal response, and this effect of mescaline is blocked by chlorpromazine.[43,44,73] Rovetta[96] has reported that topical application of mescaline chloride to the cortex of anesthetized cats failed to produce any clear effect on the amplitude of the cortical response. Pennes (to be published, referred to by Evarts[30]) has also studied the effect of topical application of mescaline to the optic cortex on cortical potentials evoked by light and by electrical stimulation of the optic nerve.

Spontaneous Cerebral Activity and the Effects of Several Drugs.—The effects of these agents in animals have been reviewed in some detail elsewhere.[30] The effects in man are of greater interest for present consideration.

Mescaline: This agent has been found to decrease the amplitude of alpha activity in man,[19] and when visual hallucinations occur the alpha activity is said to be blocked. Interestingly enough, the diminished amplitude of alpha activity persisted for several days after subjective phenomena had ceased. In psychotic patients, the percentage of alpha was found to be increased in some and decreased in others.[97] No apparent correlation between changes in the electroencephalogram and subjective responses was found.[97] In postaddicts (to narcotics) Wikler[123] found variable responses to oral mescaline (5 mg./kg.). In schizophrenic patients[24] it has been reported that mescaline given intravenously usually produced a decrease in percentage of alpha. In this same study no correlation of electroencephalographic changes and visual hallucinations were found. A decrease in delta activity is produced by mescaline.[23,78]

In a study of the effects on the electroencephalogram of mescaline, morphine, and N-allylnormorphine in 35 experiments on 21 subjects (with previous history of narcotic addiction) Wikler[123] reports that, "Clinical effects of mescaline included the production of anxiety, visual hallucinations, illusions, mydriasis, sweating, tachycardia, hyperactivity of tendon reflexes, and tremors. The frequencies of the tremors were between 6 and 8 cycles per second, and they appeared at rest and were reduced on voluntary intention movement of the affected part. Concomitantly, the electroencephalograms showed no change, intermittent or continuous replacement of alpha activity by low-voltage fast activity and/or increase in frequency of the alpha rhythms. Morphine and tetraethylammonium

chloride were ineffective in relieving the anxiety produced by mescaline. Intravenous injection of barbiturates abolished anxiety promptly."

Lysergic acid diethylamide: At the peak of the lysergic acid diethylamide (1 mcg./kg.) reaction it was found in nine experiments[90] that only slight changes occurred in the electroencephalogram, chiefly increases of 1-3 cycles per second in the alpha rhythm. One subject showed a slowing of about 2 cycles per second. Gastaut, Ferrer, and Castells[36] report that only very slight changes in general were produced in the electroencephalogram. An increase in responsiveness of the alpha rhythm as to photic driving has been reported[15,28,36] in normal subjects. Others[32] found no significant changes in the electroencephalogram in psychotic subjects on 2 mcg./kg. lysergic acid diethylamide, but psychic changes were nonetheless prominent.

N-allylnormorphine: This agent has been reported to have psychotomimetic effects by Wikler, Fraser, and Isbell,[124] by Wikler,[123] and by Lasagna and Beecher.[67] When relaxation and euphoria were produced by the drug an increase in rhythmicity and a decrease in alpha frequency was said to occur. It is reported that a decrease in the amplitude and rhythmicity of the electroencephalogram occurred when anxiety appeared.

Adrenochrome: There are varying reports of the effects of this agent on the electroencephalogram. Szatmari, Hoffer, and Schneider[118] say it does not affect the encephalogram (10 mg. dose in normals) but does in larger doses in epileptics. Hoffer, Osmond, and Smythies[54] say it does affect the electroencephalogram.

Marihuana and Tetrahydrocannabinol: Single doses had little effect on the electroencephalogram but with prolonged medication the dominant frequencies were markedly slowed.[125]

Apter and Pfeiffer[4] have studied the response of the electroretinogram of cats to lysergic acid diethylamide and on the basis of this work have concluded that lysergic acid diethylamide evokes action potentials in the retina of the anesthetized cats. They say, "These experiments demonstrate that cats are capable of having hallucinations as the result of a non-toxic dose of LSD-25." They say further, ". . . the cortical activity induced by the drug is dependent upon nervous transmission from the retina, and does not appear when the connection with the retina is severed." They ". . . conclude that the hallucinations induced by LSD-25 are not similar to illusions induced by psychosis, since the drug has a marked peripheral action." In discussion of this, Brazier[16] raises a question as to how the results might have been influenced through centrifugal efferent action on the retina.[40] In further discussion Börnstein[14] advances the view, based upon his own experimentation, that the retina is not the only region of the organism that is responsible for the occurrence of optical hallucinations.

It is evident that many difficulties lie in the path of those who would like to demonstrate causal relationship between electrophysiologic and psychologic events. Evarts[30] says, ". . . it does not appear that we have reached the point of being able to assign any particular psychological effect of the drug to a demonstrated disturbance of the electrical activity of the nervous system."

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INTERACTION OF DRUGS

The demonstration of an antagonism in vitro between lysergic acid diethylamide and serotonin has led to speculation that the in vivo effects of lysergic acid diethylamide are in actuality the result of a serotonin-lysergic acid diethylamide interaction.[30] Research in this field was greatly furthered by the finding of 5-hydroxytryptamine (serotonin, enteramine) in the brain.[34,119] The point of special interest is the role of serotonin in mental processes and the antagonism of lysergic acid diethylamide for serotonin.[127,128] (See Woolley and Shaw's footnote as to priority[129].) Gaddum,[34,35] Twarog and Page,[119] and Salmoiraghi and Page,[98] working independently, also originated and furthered this concept. Support for an in vivo antagonism has been presented by Shore, Silver, and Brodie.[103] In most cases, however, serotonin has failed to antagonize the electrophysiologic effects of lysergic acid diethylamide. Slater, Davis, Leary, and Boyd[104] did find that the effects of serotonin on a flexion reflex were blocked by lysergic acid diethylamide; the opposite effect has not been demonstrated. As Evarts[30] points out, negative evidence is not conclusive. Possibly rapid destruction of serotonin prevents the demonstration in vivo of interaction between serotonin and lysergic acid diethylamide.* Until these relationships are much clearer than they are at present, it is well to bear in mind Rothlin's[95] cautionary statement: ". . . whether there is either an interference or a causal relationship between the inhibition of serotonin and the psychic effect, is more complicated than would appear from the investigations that have been described." A well-recognized difficulty here is the fact that brom-lysergic acid diethylamide has a specific anti-5-hydroxytryptamine effect; brom-lysergic acid diethylamide is as effective as lysergic acid diethylamide in this regard, yet brom-lysergic acid diethylamide has no power to produce mental disturbances although it does produce some sedation.[95] However, as Koelle[61a] points out, it is possible that the bromanalogue is preferentially excluded by the human blood-brain barrier. The references given can be consulted for further information on the complicated subject of serotonin interactions. This controversial field cannot be fully discussed in this brief section.

Isbell[56] could find no evidence that 4-piperidyl carbinol (azacyclonol, Frenquel) could alter the psychologic effects of lysergic acid diethylamide in man. A similar "failure of correspondence" between electrophysiologic and psychologic interaction has been reported in the case of reserpine and lysergic acid diethylamide (Purpura[86,87]). Evarts[30] observes that interactions of tranquilizing and psychotomimetic drugs in animals do not permit dependable prediction of the interactions between the agents in man.

Azacyclonol, a "tranquilizing" agent, has been found to block the effects of both mescaline and lysergic acid diethylamide on the electroencephalogram in curarized rabbits.[88] Demonstration of succinate antagonism of mescaline visions has been reported by Schueler.[102] The succinate produced not only a decrease

*For extensive discussion of the chemistry involved, the role of lysergic acid as an antimetabolite, the drug antagonism involved, and mental changes produced, see the entire symposium, Ann. New York Acad. Sc. **66**:415-840, 1957.

in color intensity but also a decrease in complexity of design. He found that the mescaline "decrease in cooperation and hesitance in speech . . . [was] replaced after succinate by a more normal attitude and readiness to talk."

MENTAL EFFECTS—SUBJECTIVE CHANGES

The psychic effects are of principal concern for present purposes. Two agents, mescaline and lysergic acid diethylamide, have been more extensively studied than all others put together. Since, for reasons already mentioned, this section is intended to present typical examples rather than a thorough-going review, attention will be focused principally on these two agents. One can leave aside the centuries-old knowledge that ergot would cause grave mental derangements and come at once to 1943, when A. Hofmann, a chemist, accidentally received enough lysergic acid diethylamide to produce noticeably abnormal psychic effects and thus ushered in a new era of interest in the field of the psychotomimetic drugs.[95] The psychic effects vary widely from one man to another. The period of latency is long. Autonomic effects appear in about 20 minutes following oral ingestion, but psychic effects may take an hour and become maximal only after one to two hours.

The mental effects fall into several categories and will be discussed forthwith. Of all the mental disturbances produced by these drugs, of most importance are the hallucinations and delusions produced and the personality changes produced, or perhaps exhibited is a better word. According to Klüver,[61] Guttmann,[42] and Stockings,[111] hallucinations are common under mescaline; some authors consider them not to be very common with lysergic acid diethylamide.[90] Others, however, frequently have reported hallucinations under lysergic acid diethylamide; see below. Of all the derivatives of d-lysergic acid only three are known to produce psychic changes: the monoethyl amide, the diethyl amide, and the diethyl amide of d-l-acetyl-lysergic acid.

It is interesting to observe that dictionary definitions of hallucination and delusion do not differentiate clearly enough between them. It is necessary, then, to establish our own working differentiation. *Hallucinations* are distorted sense perceptions (visions, sounds, for example, not based on reality). *Delusions* are distorted thoughts (as "delusions of grandeur," "delusions of persecution").

Speaking of mescaline, Stockings[111] says, "It was found that the constitutional make-up in every case modified the course of the psychosis considerably." Mescaline and the diethylamide of lysergic acid (LSD) are the two most interesting agents at present and will doubtless remain of at least historical importance. While there are quantitative differences between them (for one thing the common dose of mescaline is 5,000 times greater than that of lysergic acid diethylamide) they produce in general the same effects.[53,76,90,95,115]

Hallucinations.—Hallucinations which occur while "contact with reality" is maintained presumably represent very much less mental impairment than hallucinations believed by the subject to be "real." It is regrettable, therefore, that so few authors have specified whether or not a close touch with reality is maintained during the period of hallucination. In 19 normal subjects, 10 under lysergic acid diethylamide and 9 under lysergic acid ethylamide, no loss of contact with the real situation was found by von Felsinger, Lasagna, and Beecher.[121]

It is evident that Stockings[111] in his study of mescaline deals (sometimes at least) with hallucinations during which contact *is* maintained with reality, for he says that mescaline ". . . can reproduce in the normal subject striking psychopathological phenomena without clouding of consciousness . . . ." Later on, in his review of his own experience, Stockings says, "It goes without saying that the subject of mescaline psychoses is entirely lacking in insight . . . ." (Surely many observers would equate a loss of insight with impairment of consciousness.) He says further, and what he really means begins to be blurred: "The mental changes produced are of an almost exactly similar nature to those found in psychotic patients—namely, hallucinations of all senses, delusions, transformations of personality, thought disorders, abnormalities of conduct, affect changes and disorders of temporal and spatial perception." Certainly many psychotic patients (and thus evidently some of Stockings's patients too) are out of touch with reality while experiencing hallucinations. Granting that hallucinations have similar characteristics to those found in psychotic states, "Thus their content is always in line with the subject's past mental experience. They are wish-fulfilling fantasies . . . ."[111]

Visual, auditory, and somatic hallucinations are common, those of smell and taste are rare.[111] In some 60 studies Guttmann[42] found that auditory hallucinations were rare, visual and tactile common. Mayer-Gross[76] speaks of waves of cold under mescaline. He maintained good contact with reality during his hallucinations.

Mayer-Gross,[76] Hoch,[52] and Savage[100] also emphasize the dominance of visual experiences in mescaline intoxication, especially their brilliance of color and intricacy of pattern, the persistence of after images, and the remarkable facility for visual change. Shapes of real objects alter in fascinating ways, and parts of bodies disappear (see also Guttmann[42]). Only the tactile senses and body image sensation successfully compete for attention at times with the visual for attention. Visual hallucinations predominate under lysergic acid diethylamide, as well.[115]

"The psychotic manifestations [of mescaline] occur in a state of clear consciousness."[52] The insistence of the majority of investigators on the persistence of "clear consciousness" under many of the psychotomimetic agents implies a less exact meaning of consciousness than some would prefer. In one approach, at least any drugs which produce amnesia, release self-protecting inhibitions, produce emotional disturbances, and "loosen the tight grip with which patients cling to reality"[65] could be said to have impaired consciousness. It has been repeatedly observed that hallucinations block out normal perceptions. Hallucinations are furthered by "silence, solitude and self-absorption, and mitigated or abolished by simple occupation . . ."[111]

> "The mechanism of their production appears to be as follows: The principal factor in their genesis is an enormous increase in the power of mental imagery and vividness of thought—a true hypertrophy of the imagination; thus, they commence as vivid fantasy, seen on the mind's eye, as it were, not as external objects are seen; at a later stage, when the process of mental dissociation is complete, the imaginalized thought be-

comes entirely split off from the rest of the psychic processes, and the fully-formed hallucination, appearing as a real object outside the subject, is thus produced. All the various stages between thought, vivid fantasy (pseudo-hallucination) and fully-formed hallucination can thus be seen and studied in the mescaline subject.

"Their genesis is also undoubtedly favoured by the characteristic disorder of thinking, the alteration of, and turning away from reality and the preoccupation of the subject with the novel inner life of his psychosis.

"These hallucinations are not influenced by external suggestion, thus differing from the type found in delirium tremens and allied states; the same applies to the auditory hallucinations."[111]

Fifteen normal subjects were studied under lysergic acid diethylamide (1 mcg./kg., orally) by Rinkel, DeShon, Hyde, and Solomon.[90] Disturbances of perception usually appeared within 40 minutes of the intake of lysergic acid diethylamide; they were commonly visual. The subjects realized that their experiences were illusions. No beautiful visions were seen, unlike the experiences of earlier investigators. There were frequent gustatory disturbances, a metallic taste or a "heavy tongue." In their experience hallucinations, although predominant under the influence of most phantastica were "rather meager and never showed the quality of an extraordinarily beautiful or threatening experience." Such hallucinations as they encountered were usually visual. In only one subject out of 15 was an auditory hallucination encountered. Two out of 15 experienced haptic (touch) hallucinations of wetness. Savage[100] reported hallucinations in 5 of 6 normal controls and 4 out of 14 schizophrenics.

On the other hand, Sandison,[99] for example, reports vivid hallucinations under lysergic acid diethylamide and correlates these with repressed material which is thus helpfully exposed, he believes, by the lysergic acid diethylamide.

Von Felsinger, Lasagna, and Beecher[121] report that under lysergic acid ethylamide (LAE) no hallucinations were observed, 1 out of 9 subjects merely reporting that objects "looked pallid."

Delusions.—These have been very well described by Stockings[111]: ". . . it is found that one of the characteristic actions of mescaline intoxication is that it is always accompanied by the presence of morbid suspiciousness and often of fully-developed delusions and ideas of reference, the mechanism of which can be shown in a remarkable way by means of the experimental mescaline psychosis. The delusionary ideas of the mescaline subject are of the same type as those found in psychotic patients, namely, ideas of grandeur, persecution, and bodily change. A description of the mechanism of these as elucidated in these experiments will now be given, and their points of similarity to those of psychotic patients pointed out.

"The basic factor in the genesis of the delusions appears to be a qualitative alteration of the functions of the higher cortical receptive centres, with resulting distortion of their functions, and consequent misinterpretation of external stimuli. The delusions are thus dependent primarily on a disorder of the central perception organs, especially the auditory centres.

"Taking first the delusions of persecution, we find that one of the characteristic actions of mescaline is that of sensitization of the auditory

centres. Sounds appear to be either unnaturally loud, or distorted, and to have acquired strange qualities. They appear to the subject to rush upon him in an extraordinarily purposive and deliberate way, and to have a reference for him which they would not have in the normal state. Thus, to quote actual examples, seen in the writer's experiments, the sound of a typewriter being used in the next room seemed to vibrate and reverberate through the walls and into the subject's body; thus, the typewriter became an infernal machine persecuting him with rays of electricity; in another case a group of people talking in the next room becomes a gang of enemies plotting against him or interfering with him. Similarly, the announcer's voice is sending messages over the wireless specially meant for him.

"In the visual sphere, the strange distorted appearance of people's faces, their movements and conversation all seem to be directed against him, so that he feels as if he was being watched, spied upon or otherwise interfered with.

"Similarly, the strange bodily paraesthesiae readily produce ideas of influence, electrical interference, or bodily changes produced by the machinations of other persons.

"This delusionary state may vary from morbid suspiciousness to fully-developed ideas of persecution, according to the stage of intoxication and the surroundings of the subject. It is apparent that persecutory delusions require some stimulus, in the form of an auditory or visual perception, for their production.

"Grandiose delusions may arise in two ways. One is from the somatic paraesthesiae. One of the commonest of these is a feeling of having grown extremely tall and handsome, and of being possessed of superhuman strength. Appreciation of the weights of objects is always disordered, and common objects may seem extremely heavy to the subject; in this way he imagines, for instance, that in raising a chair he is lifting an enormous weight. The hallucinations of supernatural figures and voices similarly give rise to ideas of communion with God, and of being divinely inspired.

"In these last types of delusions, the disorder of thinking and of association and lack of insight are important contributory factors in their production.

"The striking similarity of the delusional states thus described to those found in schizophrenic and delusional cases will at once be observed."

Hoch[52] has confirmed the findings of others concerning mescaline's effects and reports as common ". . . paranoid, grandiose or hypochondriacal delusions; misinterpretation of environmental situation."

Under lysergic acid diethylamide (1 mcg./kg.), Rinkel, DeShon, Hyde, and Solomon[90] did not observe major delusions as a grandeur or persecution in their normal subjects.

Disturbances of Thought and Speech.—These have been well described by Guttmann[42] and by Stockings.[111] Stockings says:

"The characteristic symptom [of mescaline] is a peculiar slowness and difficulty of thinking, a divorcement of the intellectual functions from the rest of the cerebration, with, simultaneously, a greatly increased output of spontaneous fantasy and imagery. Incoherence and thought-blocking are well shown, and give rise to the peculiar disorders of lan-

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guage presently to be described. Flight of ideas, as in the manic states, may occur as a principal feature, or in combination with blocking of thought on the intellectual side. The subject may complain of strange and foreign thoughts being put into his mind, or that each thought is simultaneously repeated as either an auditory or visual perception—the phenomenon of 'double thought' so well exemplified in schizophrenic states. The feelings of passivity, of thoughts foreign to the subject being put into his mind from outside and ideas of influence are also well-known schizoprenic symptoms. Inability to hold a train of thought and follow it up to its logical conclusion, and perseveration and ideational inertia with disorders of association, are also found. A characteristic symptom is that there are several different simultaneous trains of thought running parallel in the mind of the subject. The thought-content is dominated by the subject's particular complex, as in schizophrenic states. The peculiar scattered type of thinking and volitional disorders are at once strongly reminiscent of schizophrenic phenomena, while the psychomotor retardation and flight of ideas bear a striking resemblance to the symptoms found in the depressive and manic psychoses respectively.

"The characteristic change appears to be the peculiar divorcing of the intellectual part of the personality from the rest of the psyche, with disturbance of association, blocking of voluntary intellectual thought, and extreme distractability. These factors, combined with the morbid suspiciousness and non-co-operativeness of the subject, render any proper assessment of the state of the intellectual functions extremely difficult. It is known that the mental efficiency, as measured by psychological tests, shows a great falling-off in performance. The subject can only perform the simplest tests and remember the most elementary facts from his past store of knowledge. The time taken for the performance of any test is increased, and the number of mistakes is also greatly increased."

Thought seems [on occasion] to progress at amazing speed under both mescaline and lysergic acid diethylamide and, at the same time, memory is defective for the recent past.[52,111,115] Doubtless, these effects account at least in part for the disturbances of time sense, discussed below.

"The subject's comprehension of, and memory for, the actual events taking place in the outside world during the period of his [mescaline] intoxication is good; but upon return to normality there is almost complete amnesia for the mental experiences, with the exception of one or two of the more striking hallucinatory scenes. The auditory hallucinations are always much better remembered than the visual. This amnesia for the mental experiences of the psychosis, with a good memory for the actual events in the world of reality, was a striking finding in many schizophrenic cases observed by the writer."[111]

The most prominent psychologic changes observed by Rinkel, DeShon, Hyde, and Solomon[90] in 15 normal subjects under lysergic acid diethylamide (1 mcg./kg., orally) were in thinking and speech. In general, these effects appeared in 30 to 45 minutes and cleared in 3 to 4 hours. There was no clouding of consciousness, they say, and no intellectual weakness, but difficulty in power of expression was frequently observed. "The subjects became more and more slowed down, poverty of thought became apparent, and the flow of speech became increasingly disso-

ciated and blocked." Presumably the reason these authors are so certain no clouding of consciousness recurred was that the subjects could clearly recall the next day all events that occurred during the phase of impaired speech, and ". . . each one was able to give, in a written report, a description of all the experiences he went through."

> "Hesitancy, indecision, and impairment of abstract thinking were frequently present; also looseness of thought and actual disconnection with increased distractibility were common observations." "Gross clouding of consciousness was absent in our experiments, but illusional misinterpretations were not infrequently observed."

One subject out of 15 demonstrated accelerated thought with flight of ideas associated with rhyming and punning. In this instance garrulity and loquacity were like that seen in hypomanic individuals.

Synaesthesia, "colour-hearing and sound-seeing," are reported as characteristic mescaline phenomena.[42,52,76,111] In no instance in 15 normal subjects under lysergic acid diethylamide (1 mcg./kg., orally) did Rinkel, DeShon, Hyde, and Solomon[90]) elicit synaesthesias. They agree that synaesthesias are common under mescaline.

Von Felsinger, Lasagna, and Beecher[121] report no increase in thought or speech processes in their 10 normal subjects under lysergic acid diethylamide, but rather a slowing down of speech and expression, with confusion, difficulty in concentration and in remembering what was read. Eight out of 10 reported difficulty in "paying attention." Lysergic acid ethylamide produced "dulling of thought" in 7 out of 9 cases and also difficulty in concentrating.

Disturbances of Time and Space.—Mescaline acts like cannabis indica, morphine, and cocaine to slow down the passage of time.[42,76,111] With a "small dose," 0.2 Gm. by mouth, this may be the only change perceived; with a large dose, 0.4 Gm. by mouth, mental dissociations occur, and the individual may believe that he is traveling backward or forward in time, or that ". . . in the course of a single afternoon he has lived through thousands of years."[111]

In 11 out of 17 experiments (15 subjects) Rinkel, DeShon, Hyde, and Solomon[90] found that lysergic acid diethylamide (1 mcg./kg., orally) disturbed the time sense, sometimes accelerated, sometimes retarded.

Characteristically, mescaline produces disturbances of space perception.[42] According to Stockings,[111] "Thus, rooms appear as huge fantastic chambers, or endless corridors, and the walls and floor appear to have changed their shape."

Depersonalization.—Alteration of personality is the "basic and fundamental" symptom of the psychosis produced by mescaline.[42,52,76,111] If schizophrenia is literally a split mind, Stockings believes that mescaline temporarily produces it.

> The subject's belief ". . . that something has been taken away from his personality and something strange and foreign substituted, is characteristic. The change consists of a radical alteration of the mind and body. Thus, the subject may feel that he is being several different persons at once—a symptom sometimes found in schizophrenia. More characteristic still is the feeling that he is divided into two separate beings—one purely intellectual and emotionless creature, the other a

> fantastic being of delusion and fantasy, the first being able to observe the other in an extraordinarily detached and unemotional fashion.
>
> "A further feature of the personality changes must be mentioned before leaving this subject, namely, the symptom of transformation of the personality—that is, the belief that the patient has been changed into someone else. Thus the subject of the mescaline psychosis may believe that he has become transformed into some great personage, such as a god or a legendary character, or a being from another world. This is a well-known symptom found in states such as paraphrenia and paranoia. As found in the mescaline psychosis, it appears to be due partly to the abnormal bodily feelings referred to in the discussion of delusions of grandeur."

Under lysergic acid diethylamide[76,90,100,121] depersonalization occurred frequently. Often parts of the body were suddenly abnormally large or small or disappeared altogether. The most common feeling was one of unreality for the subject himself and for the outside world.

Mood Changes Effected by Drugs.—Euphoria or dysphoria or depression can be produced by mescaline, depending on the stage of the intoxication.[42,111] Unlike the common sequence of events with alcohol, depression characteristically appears early in the psychosis. "It takes the form of an acute agitated type of depression, associated with intense anxiety and fear, and a sense of impending dissolution. There may be also ideas of unworthiness, of being irretrievably damned and lost, and of intense hopelessness. Associated with this is a terrifying feeling of unreality of self and of the outside world. Objects take on an extraordinarily sinister and vaguely menacing appearance."[42,52,111] Guttmann[42] reports that mescaline is not aphrodisiac, on the basis of his own studies as well as those of others.

Euphoria in response to mescaline appears to be a consequence of direct central action not consequent to the effect of pleasing hallucinations.[111] Emotional instability and fatuousness are common. "The mescaline subject also shows incongruity of affect, with complete indifference to events in the outside world, towards which he displays markedly shallow affective response. Thus, he may simply laugh fatuously at a piece of bad news; or he may wear a mournful and depressed expression whereas he is really inwardly elated and exalted; or he may laugh fatuously while in the depressive stage."[111]

Waves of elation and dejection rapidly alternated under mescaline.[111] This is also true for lysergic acid diethylamide where a periodic or wavelike alternation characterized many of the responses to lysergic acid diethylamide.[121]

Within 15 minutes under lysergic acid diethylamide (1 mcg./kg.) Rinkel, DeShon, Hyde, and Solomon[90] found that "feelings of indifference and blunting tended to be protracted; suspiciousness, hostility, and resentment were always more transient. Changes in mood were twofold: euphoria and depression, which occurred in about equal number." They say further: "In no instance did we observe the happy and dreamy feeling of ecstasy as it has been described by other authors who experimented with L.S.D., mescaline, and other similar chemicals."

In study of "more than 100" normal males and females under lysergic acid diethylamide (1 mcg./kg.) Rinkel, Hyde, Solomon, and Hoagland[93] expressed

particular interest in hostility. They say, ". . . strongly affective relationships of affiliative or hostile nature were distorted to a greater proportion (26%) than were relationship of impersonal, emphathic and nuturient character (6%)." Lysergic acid diethylamide appears to intensify interpersonal relationships.

In the realm of behavior under lysergic acid diethylamide, presumably influenced by mood, Rinkel, Hyde, Solomon, and Hoagland[93] report:

> "Our sociologist, Morimoto, investigated the sociopsychological behavior of 43 normal subjects who were under the influence of LSD. An evaluation was made on each subject before he received LSD, as a basis for comparison. Each subject was classified on 35 attributes which indicated feelings and actions related to his behavior in interpersonal relationships. These attributes were further classified into 4 categories or modes which indicated in which directions one moves in interpersonal relationships. The modes of directions were: away, against, toward, and with.
>
> "The results of this intriguing study revealed that during the influence of LSD the scores in the modes, away, against, and toward, were significantly increased (x^2 significant at .001 level). A significant decrease in scores was found in the "with" mode (x^2 significant at .001 level). These observations mean that the behavior of the subject who is under the influence of LSD is altered from his pre-LSD behavior in the sense that the mode is now one of the moving *away* (avoidance, withdrawal, denial); *against* (hostile, punitive, competitive); and *toward* (seeking of nurturance, support, reassurance); while the *moving with* (brotherly, friendly, reciprocal equalitarian) type of behavior is clearly reduced. This study also indicated that the hospital personnel had more severe reactions than subjects from outside of the hospital. The ability to mobilize appropriate social behavior was reduced during LSD; the directions of change were toward greater rigidity, although a few exhibited an erratic and overreactive type of behavior (x^2 significant at $>.05$ $<.02$ level). Intensity of symptoms subjectively experienced increased in social situations in which there were specific expectations placed upon the subject (x^2 significant at .001). On the other hand, intensity of symptoms was reduced in those social situations that were supportive and nurturant to the subject.
>
> "One cannot escape the impression, from these observations, that the sociopsychological behavior changes showed similarities with the general behavior of the mentally ill and that they provide fundamental implications in the field of psychotherapy."

Loss of emotional control was common under lysergic acid diethylamide.[90] But no consistent trends toward anxiety and tension were found, ". . . possibly because of the peculiar nature of the experience *which preserves insight* in spite of drastic intellectual and emotional changes."*

Comparison of lysergic acid diethylamide and lysergic acid ethylamide: The latter agent has been comparatively little studied. In this, the experiences of von Felsinger, Lasagna and Beecher[121] partly confirm those of Solms.[110] The doses of lysergic acid ethylamide (3 were given 0.25 mg. and 6 were given 0.5

*Italics mine.

mg., subcutaneously) utilized by them were many times greater than those of lysergic acid diethylamide, but no striking difference in severity of symptoms was seen. This confirms Solms's statement about differences in potency. The data[121] on perceptual distortions also suggest that Solms's second statement about the rarity of optic "hallucinations" after lysergic acid ethylamide (as compared with lysergic acid diethylamide) is similarly correct. His third differentiation (relative to differential mental effects), however, cannot find full confirmation in the new data. Both lysergic acid ethylamide and lysergic acid diethylamide seem to produce a general slowing down of mental processes in these subjects. Both drugs show remarkable power in producing definite psychologic changes. These changes are not unique in the experience of this laboratory and other drugs have produced symptoms of even greater degree, but the incredibly small traces of lysergic acid diethylamide that are sufficient to effect change are of considerable significance. Those investigators who choose to view these drug reactions as "schizophrenic" see in this fact considerable support for the conception of schizophrenia as an endotoxicosis. The experience of von Felsinger, Lasagna, and Beecher[121] with the monoethyl amide of lysergic acid, while limited, does not give much support to such a view since with one exception (suspiciousness) the symptoms observed under this drug are not unlike those produced by other agents and do not, clearly, constitute psychotic processes to any greater extent than those produced by other drugs: in this regard it seems important to emphasize the maintenance of voluntary control and, more particularly, of insight and the capacity for reality testing throughout the drug reaction by these subjects.

Four of 10 subjects under lysergic acid diethylamide (usually 1 mcg./kg., p.o.) experienced increase in anxiety; two of these laughed out loud or smiled for long periods.[121] Two of the 10 had erotic sensations.

Rather striking hostility with paranoid tendencies in 4 out of 9 subjects was found under lysergic acid ethylamide (LAE) by von Felsinger, Lasagna, and Beecher.[121] Three considered their reactions pleasant, and 3 considered them unpleasant. One of the latter had a panic reaction with intense fear. One subject of the 9 reported an "overwhelming desire to talk." Five of the 9 felt amused or laughed out loud. As with lysergic acid diethylamide recurrence of symptoms in "waves" was observed.

PHYSICAL EFFECTS, INCLUDING OBJECTIVE CHANGES

Autonomic (Vegetative) Disturbances.—Mescaline appears to have a specific action in abolishing sleep.[111] There is also restlessness and profound anorexia. Sexual function is depressed.[42]

Lysergic acid diethylamide produces numerous disturbances of the autonomic nervous system.[42] Rinkel, DeShon, Hyde, and Solomon[90] report:

> "The most common symptom was change in appetite, which more often was decreased, and associated with nausea, than increased. Complaints of headiness, giddiness, faintness, tremulousness, and shaking were frequently expressed. The subjects complained of chilliness and coolness of whole or part of the body, lump and "funny" feelings in

abdomen, constriction with oppression in chest and precordial discomfort, violent cramps and constriction in the abdomen in a patient who just happened to menstruate. Objectively observed were flushing, sweating, shivering, with goosepimples. Tachypnoea, salivation, pallor, sighing, and urgency of micturation were scattered observations. Changes in pulse rate and blood pressure were of minor magnitude and observed only occasionally. Involuntary smiling, giggling, or laughing were considered in the nature of "risus sardonicus" where the subject described these phenomena as occurring without or against his will. One subject stated that in a smile he felt as if his facial muscles were like plastic wax being moved by some inexorable force. Pupils were often maximally dilated."

In studying lysergic acid diethylamide Rinkel, Hyde, Solomon, and Hoagland[93] report on subjective experiences:

"All subjects who had taken LSD experienced sensations which were the result of dysfunctioning of the muscular, cutaneous, gastrointestinal, genitourinary, cardiovascular, respiratory, and sensory systems. Most common were subjective feelings of trembling, while actual tremor was rarely seen, feelings of numbness, hunger, and nausea; less common were coldness and warmth, perspiration, tingling, throbbing, flushing, sighing, tightness, choking sensation, sexual excitement, and need to urinate."

Physical measurements of pupil size, heart rate, blood pressure, and respiration showed that the heart rate was more stable on lysergic acid diethylamide days than on placebo days, the respiration more variable and the pupils larger. Blood pressure was in general little affected by lysergic acid diethylamide; there was, however, a notable rise in blood pressure under lysergic acid diethylamide following "psychiatric interview." They[93] found further that lysergic acid diethylamide did not significantly alter the response of the autonomic nervous system to norepinephrine, whereas epinephrine was less effective than normal in producing a rise in blood pressure under lysergic acid diethylamide. (These experiments were carried out on mental patients.) Experimental work of this group indicates that lysergic acid diethylamide stimulates the pituitary adrenal axis.

Rothlin[95] concludes that ". . . in the animal, a central sympathomimetic syndrome predominates and that psychic changes are probably present, but difficult to interpret [under lysergic acid diethylamide]. In man psychic changes predominate, while the autonomic symptoms are apparently subordinated."

Motor Disturbances.—A "disinclination for active movement" is common under mescaline.[52,111] Sometimes catatonic states, even, are produced. Such quiet states may alternate with outbursts of aimless motor activity. There is indifference to pain which, though perceived, is not reacted to.

Under lysergic acid diethylamide[90,93] the most striking change found in 15 normal subjects (1 mcg./kg.) was underactivity with lack of spontaneity and initiative. However "psychomotor manifestations, such as smiling, giggling, and laughing, more often appropriate than inappropriate, were frequently observed."

OBJECTIVE EXPERIMENTAL MEASUREMENT

Rorschach.—When the same subjects were given Rorschach tests in their normal state and then under mescaline, it was found, surprisingly,[122] that the latter corresponded closely with the personality as known in normal life; the former was very different and revealed a personality that had been hidden.

Guttmann,[42] working with Vernon, on mescaline, concluded on the basis of Rorschach tests merely that the personality had "changed." He chose not to interpret his data beyond emphasizing that they indicate the "importance of the perceptual sector of the personality."

Stoll[117] found in 11 normal subjects under lysergic acid diethylamide that the Rorschach changes show typically ". . . a general loosening of mental processes . . . [with] disinhibition of affectivity and fluency of thought processes, of which the precision and wealth of contact, however, is decreased." Five subjects were subjected to such study while under lysergic acid diethylamide (1 mcg./kg.) by Rinkel, DeShon, Hyde, and Solomon.[90] All tests showed abnormalities "principally of the schizophrenic or paranoic type." "There was noticed autistic thinking with decreased organization, contamination responses, and lack of logical thinking, also negativism and diminished emotional inhibition indicating anxiety, depression, and aggression. One Rorschach test revealed a moderately schizophrenic picture with autistic thinking and withdrawal."

In another report,[93] Rorschach tests were performed on 29 subjects (these were partial tests, Cards III, VII, and VIII being used.) All but 2 subjects showed significant change under lysergic acid diethylamide from their normal state. In addition, Wechsler-Bellevue Block Designs (No. 2 and No. 4), a Draw-a-Person Test, and 8 Thematic Apperception Cards were used. For the group as a whole the most marked change they found was ". . . a definite reduction in organization and integration of the subjects' response to conventional features of their environment and experience. They showed a lack of concern about their behavior and responses. Their disregard for the environmental stimuli was accompanied by an increased concentration on discrete or minute aspects of experience. The subjects' attention was centered on restricted areas. There was a general loosening of critical appraisal. Intellectual control was impaired with difficulty in concentration and associative thinking."

Von Felsinger, Lasagna, and Beecher[121] carried out fairly extensive Rorschach studies under lysergic acid diethylamide and under lysergic acid ethylamide. Their observations are as follows:

"I. *Lysergic Acid Diethylamide (LSD)*

"All 10 lysergic acid diethylamide subjects were given a second Rorschach examination while under the effects of drugs. The first Rorschach examination was given before the drug was administered, as previously described. These tests were given usually several hours after the drug ingestion when the observers believed the symptomatology was either at its peak or just receding. Seven of the 10 subjects showed distinctive changes in the determinants of their responses. [In an extensive study of the so-called ego-depressant drugs, this is the first time they had found a fairly consistent modification of the Rorschach response by

drug.] In six of these seven cases the changes were in the same direction and of similar meaning. In general, these changes took the form of an expansive release phenomenon in which the postdrug Rorschach was an exaggerated caricature of the predrug one, whereby previous weakness of ego functions was particularly magnified. Intellectual processes tended to regress to an immature level. Thus animal movement responses (FM) became dominant over human movement responses (M). This was particularly evident where the predrug balance was stable or M not especially dominant. Since M dominance is a normal concomitant of mature development, this reversal indicates regressive and immature thought processes, as well as a weakening of intellectual control over affective and emotional impulsivity. In adults, too, the degree of FM dominance correlates with the degree to which productive potential is wasted. The same regressive phenomenon is reflected in the shift in color responses from FC to CF and in a few cases, to C. In adults FC responses should be dominant. They reflect the development in behavior of increased restraint in the regulation of the forms of self-expression, and the modulation and restriction of the behavioral and emotional impulsivity and unpredictability characteristic of younger age groups. These postdrug changes seriously undermined the characteristic mechanisms developed by each personality for the control of behavior and for defense against anxiety. Under these conditions perceptual processes were correspondingly altered with an accentuation of emotional states at the expense of external reality factors. The fact that only three subjects of these seven experienced sensory illusions seems surprising.

"The M:ΣC ratio, reflecting the balance of affective and regulatory spheres in the personality (optimally within 2:1 to 1:2 range), was seriously unbalanced under the drug, the median ratio for the seven cases being 1:3.5 and 0:7.5 following the drug. This severe threat to self-control was reflected in the experience of tenseness, anxiety, and 'jitteriness,' as well as the stated fear of losing control.

"As indicated above, the degree to which the Rorschach was changed was positively correlated with the relative weaknesses of personality development already present. Significantly too, the total amount of reaction to the drug (in terms of objective evidence and subjective description) was also highly correlated with a 'maladjustment' ranking by the psychologist based on an interview and the predrug Rorschach test. The correlation between these maladjustment rankings and the drug reactivity rankings by the pharmacologist was .93. Rankings by the pharmacologist and by the psychologist were performed independently of course."

Case examples are given to illustrate what seems to be a primary psychologic effect of the drug—the exacerbation of existing symptomatology through a weakening of control functions and defense systems.

"II. *Lysergic Acid Ethylamide (LAE)*

"Predrug Rorschach testing and interview were given to seven of the nine lysergic acid ethylamide subjects. Again independent ranking by the psychologist and pharmacologist revealed a high correlation (.80) between 'maladjustment' and degree of drug 'reactivity.' The three best adjusted individuals (ranks 1, 2, 3) had no, or extremely minor, effects, and this group of subjects did not scatter so widely along the adjustment-maladjustment continuum as did the lysergic acid diethylamide subjects.

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> "The range of reactions and particularly their intermixture in this small sample precludes the analysis of drug reaction and personality structure. However, the four subjects who had paranoid or hostile reactions to lysergic acid ethylamide and the single subject responding in like manner to lysergic acid diethylamide deserve special comment, since the reaction has not been seen (when consciousness was unimpaired) in this laboratory during the study of other drugs. An analysis of the pre-drug Rorschachs (on four of the five) indicates that while none of them could be called 'paranoid' (except by analytic implication from homosexual trends in two of them) the incidence of 'looking,' 'watching,' and 'eyes' responses in essentially guarded records is suggestive of suspicious attitudes in interpersonal relations. While this implies psychologic predisposition it is noted that one of these subjects had participated in other drug experiments involving five drugs and this reaction had never been noted. He was, however, atypical in his reactions to several of these drugs, where uniformity of reaction was more common among subjects than in the present experiments."

Psychomotor Tests.—Psychomotor tests carried out under mescaline in Guttmann's laboratory[42] were characterized chiefly by the increased incidence of errors made.

No details are given but it has been reported by Rinkel, DeShon, Hyde, and Solomon[90] that lysergic acid diethylamide (1 mcg./kg.) produced in this area a "wide range of responses in abstraction and over-generalized and tangential thinking," similar to those encountered in schizophrenic patients.

Lasagna, von Felsinger, and Beecher[68] have pointed out that "the nature of the subject and the situation in which a drug is administered are important determinants of drug effects," not the drug's "pharmacological" properties alone. This is especially striking in the domain of subjective responses.

Kornetsky, Humphries, and Evarts[62] in a carefully controlled study set out to test in 10 volunteers the hypothesis that "the magnitude of drug induced psychological effects is significantly related to the reactivity of the subject." They considered four classes of centrally acting drugs: meperidine hydrochloride 50 and 100 mg., secobarbital sodium 100 and 200 mg., chlorpromazine hydrochloride 200 and 400 mg., later 100 and 200 mg., lysergic acid diethlyamide 50 μ and 100 μ and two placebos. All agents were administered orally as unknowns ("double blind" system).

A battery of psychomotor tests was presented to each subject who eventually received all drugs and placebos. Lysergic acid diethylamide affected performance on more tests than any other drug but did not significantly affect the pursuit rotor tests (this is in agreement with Abramson, Jarvik, and Hirsch[2] and Jarvik, Abramson, and Hirsch[58]) suggesting that lysergic acid diethylamide has little effect on motor coordination but rather great effect on perceptual and intellectual processes. Chlorpromazine and secobarbital affected complex intellectual tasks (but not simple ones) and also affected motor coordination. However, Landis and Clausen[66] report in schizophrenic patients, impairment on some motor tests and increased critical flicker fusion thresholds under lysergic acid diethylamide. Mescaline usually resulted in lowered motor tests and lowered critical flicker fusion scores.

Kornetsky, Humphries, and Evarts[62] conclude that the "effects of drugs on psychological performance in man are due not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject and to an interaction of the two. There is not a significant correlation between the objective and the subjective psychological effects of a given drug. However, the drugs that produce the greater mean objective effect also produce the greater mean subjective effect."

In a further report on this same subject material they found[63] when they examined the data derived from the Minnesota Multiphasic Personality Inventory that "The Depression and Psychoasthenia scales correlated significantly, or almost significantly, with the subjective effects and, to a less extent, with the objective effects of those drugs and dosages that produced significant effects." They say further, "These results support a hypothesis that personality plays a role in determining the extent of drug effect." Thus they support the similar view of von Felsinger, Lasagna, and Beecher.[120]

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PART III: CONCLUSIONS

GENERALIZATIONS AND SOME QUESTIONS

Results Expected From Work in This Area.—Guttmann[42] discusses what is gained by a study of mescaline:

> "(a) A new aspect of disintegration of sensory function, namely in the direction towards synaesthesiae. (b) A new idea of the importance of the perceptual sector within the personality. (c) Some therapeutic prospects, especially with regard to depersonalization states. (d) An opportunity of experiencing undescribable mental changes as a help in understanding the mental life of schizophrenics—a point so important for psychiatrists.
>
> "For the future it may be expected that experimental work, as previously outlined, may lead to a better understanding of the complicated interplay of aetiological factors in the origin of psychoses. Careful analysis of one intoxication like mescaline promises a reliable basis for knowledge in the field of toxic psychoses generally, and perhaps hints for the solution of the great problem of psychiatry, that of schizophrenia."

In discussing what is gained from experimental study of drug psychoses, Mayer-Gross[76] emphasizes, as some have before[79,116] and others since, that the pychiatrist as a result of such self-experimentation gains the advantage of increased insight into the problems of deranged patients.

One hopes, of course, that production of the symptoms of mental disease will make it possible to study profitably the mechanism of their production[100] and that these drugs, especially lysergic acid diethylamide, will be useful in the therapy of mental illness.[6,21,100,115]

Persisting Difficulties.—Drug studies in this area are notably unsophisticated in many cases, from the point of view of design, that is, the use of the double unknowns technique and of placebos, the separation of subjects so that they cannot "condition" each other as to what to expect, the use of randomized data,

of correlated or cross-over data, control of possible interaction of drugs, mathematical validation of supposed differences—these essential safeguards are more often ignored than observed. It is rather paradoxical that observers who are most familiar with the complexities of the human mind should pay so little attention to the self-evident difficulties of drug evaluation in this area. The needless waste this inevitably leads to in terms of money, time, and human misery is worth more attention than it has so far received.

In a quotation recorded earlier from Rinkel, Hyde, Solomon, and Hoagland,[93] the comment was made that their hospital personnel when acting as subjects had more severe reactions (behavioral) than subjects from outside the hospital. This arouses suspicion that the hospital personnel had, through intimate contact and discussion with each other, produced a certain amount of "conditioning" which led to this difference. Von Felsinger, Lasagna, and Beecher[121] ran into this problem even when using outside subjects who by coincidence happened to be roommates. The use of personnel who are in communication with each other is likely to lead to distorted and unsound observations.

Drugs which cause psychoses, notwithstanding their wide chemical and pharmacological diversity, give rise to a well-recognized pattern well-described by Hoch, Pennes, and Cattell.[53] It is hazardous to attribute specificity to a given drug or a given group of drugs.

> "The acute organic syndrome (acute toxic reaction, acute delirium, toxic-infectious psychosis, infective-exhaustive psychosis, etc.) following drug administration is basically similar to that produced by other noxae and consists of the following features: 1) Mental clouding with impaired consciousness and fluctuating attention, grasp, retention, and orientation; 2) Perceptual disturbances, mainly visual and auditory illusions and hallucinations; 3) Emotional lability, usually with some degree of anxiety, suspicion, brooding unrest, euphoria, or indifference; and finally 4) Aberrant behavior of various degrees of organized motor activity consistent with the remainder of the reaction. The essential feature for the diagnosis of the syndrome is the presence of the mental clouding and the confused state; the other components may or may not all be present in a given case."

The subject material, whether sick or well, modifies the results observed. In frank schizophrenia, mescaline accentuates the symptoms. In latent schizophrenia the drug precipitates schizophrenic psychoses (Hoch[52] and others). So also lysergic acid diethylamide accentuates pathologic processes already present (Savage[100] and others).

Rinkel, DeShon, Hyde, and Solomon[90] "mention the similarities of the experimental [psychotomimetic] phenomena to actual psychotic states in order to caution against fallacies that may occur in the interpretation of experimental psychotic disturbances. The same caution that is warranted in the application of an animal experiment to a pathological condition in man is needed in the application of the psychiatric experiment to natural psychosis." They continue, "We must bear in mind that, in addition to d-lysergic acid, a great variety of seemingly unrelated chemical substances are capable of producing transitory psychotic-like symptoms."

Some Questions.—There are a number of questions[53] which arise from a survey of the psychotomimetic agents.

Are the symptom patterns characteristic for each drug or each type of drug? The answer to this appears to be that some drugs, notably mescaline and lysergic acid diethylamide, give rise to symptoms which in many respects are similar to those of the toxic psychoses rather than to the acute organic reactions. As indicated above, mescaline and lysergic acid diethylamide typically produce in normal subjects "a hallucinatory-illusional state with emotional changes but without impairment of orientation, comprehension, and memory."[53] These are the findings in the majority whereas only the minority exhibit acute organic reactions to many of the other types of intoxicants.

It has been fairly generally agreed upon that the psychotomimetic drugs do not evoke specific symptoms related to a single drug but do call out general "acute exogenous reactions." It is customary to explain differences among individuals as arising in the person involved, in his conditioning, in his situation. Solms[109] considers the factors just mentioned to be inadequate to explain all of the individual differences encountered as, for example, the differences which appear under three similar ergot derivatives: the mono and the diethyl amides of lysergic acid and lysergic acid amide. He has therefore studied the question of relationship between the chemical structures of these compounds on the one hand and certain subjective responses produced by them on the other hand.

Solms concludes[109]:

> "There are, then, no principal differences in the mental symptomatology produced by LSD and LAE. Both drugs can bring about the same symptoms, but in general one can say that LAE produces lethargy, indifference, drowsiness, apathy, and abulia more often than does LSD. The deterioration of consciousness is slightly greater with the use of LAE. Finally, the hallucinatory phenomena, which are exceptional with small doses of LAE, become frequent, intensive, and impressive (as always with LSD) with high amounts of LAE. . . . The effective doses of LA are the same as for LAE, but LA induces greater indifference, a decrease in psychomotor activity, and a desire to sleep much more strongly than does LAE, until finally an increased clouding of consciousness produces sleep. LA may provoke sleep after one-half to one hour; if the subject is not awakened, sleep lasts approximately two hours. If the dose of LA is increased, no certain hallucinatory experiences can be noticed, but uncomfortable autonomic disturbances do occur, such as, hypersalivation, emesis, dizziness and diarrhea; sometimes irritative depressive moods occur concomitantly. Because of these symptoms the tolerance point was considered reached." Solms then interprets his data as follows:
>
> "Using the greatest prudence the following provisory interpretations are proposed. If ethyl groups are substituted on the amide group of LA, its power to produce hallucinations seems to increase. On the contrary, if the number of substituted ethyl groups [is] decreased, hallucinatory potentials are also weakened; i.e., the visual system seems less affected, but psychomotor activity decreases and clouding of consciousness is augmented until sleep occurs."

He has labeled this approach "comparative pharmaco-psychiatric analysis." The trouble is, no indication at all is given as to whether the most elementary safeguards were observed to control the highly subjective observations made. This approach must of course be used. Surely one day it will be recognized that if sound judgments based upon subtle observations like these are to have meaning, they must be protected by controls not evident in this study.

What individual factors influence reaction to psychotomimetic drugs?[53] In this poorly defined area individual susceptibility and personality type seem to be important (quantitative data here would help greatly). Pennes[53] studied the responses of a group of schizophrenia patients to four agents, amobarbital, "pervitin," mescaline, and lysergic acid diethylamide. He found that 28.8 per cent of the group reacted (presumably the same patients with each drug) with intensification of symptoms. He called these "intensification reactors."

How do psychotic subjects react to drugs which produce psychotic states in normal individuals?[53] A great deal of attention has been devoted by many investigators to answering this question.[53,90,95,115] The major observations have been usefully summarized by Hoch, Pennes, and Cattell[53]:

> "(a) The majority of schizophrenics displayed intensification of their pre-existing symptomatology on administration of mescaline or LSD25; pervitin (desoxyephedrine, methyl benzedrine) was somewhat less effective as an intensifier of abnormal mental phenomena, while sodium amytal was the least effective intensifier of the four drugs employed. (b) The reactions of schizophrenic patients to mescaline and LSD25 are usually marked with severe anxiety and other emotional patterns while disorganization of thought and behavior patterns may be profound. (c) Mescaline psychosis in normal individuals bears only a partial resemblance to natural schizophrenia. . . . The point has been made that chronic administration of mescaline might elicit a reaction more closely approximating the chronic schizophrenic state but the necessary experiments have not been reported. Of the earlier workers, Stockings . . . and Bensheim . . . felt that schizothymic and cyclothymic individuals reacted differently to mescaline. However, Beringer in his exhaustive 1927 monograph was forced to the conclusion that there was no correlation between the previous personality and the reaction to the drug in normals. . . . It would seem, however, that schizophrenic patients do react differently to the drug from normals. In general terms, schizophrenics display severe anxiety and intensification of their original thought and behavior disorganization, whereas normals usually do not pass into a frank schizophrenic episode. In terms of reality control, schizophrenics respond to the intoxication with a further disruption of their faulty reality-handling mechanisms whereas normals tend to cope with the intoxication in a basically adequate fashion."

Is there a relationship between perceptual and emotional changes following administration of mescaline or lysergic acid diethylamide? Hoch, Pennes, and Cattell[53] summarize their wide experience:

> "(a) In the majority of subjects the appearance of anxiety was concomitant with the onset of the perceptual abnormalities. Both the form and content of these perceptual abnormalities apparently served to generate a reactive or secondary anxiety. Apart from this general

relationship, little appeared that could be correlated in a more specific way. For example, (b) different subjects had different emotional reactions (anxiety, depression, hostility, suspicious-paranoid) despite perceptual experiences of the same form. (c) There was often no evident correlation between the apparent intensities of the perceptual and concomitant emotional experiences in different subjects. (d) And finally the same individual on repeat administration of the drug could in some cases experience approximately the same type and degree of perceptual change with a decreasing or qualitatively different emotional reaction.

"It is apparent therefore that perceptual changes may be correlated with the effective responses in acute mescaline or LSD25 psychosis but the relationship is neither qualitatively or quantitatively direct or specific and often appears to involve higher level symbolic reactions. The autonomic and sensori-motor reactions to these drugs are also extremely difficult to correlate with the remainder of the response, either qualitatively or quantitatively."

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If the psychosis producing drugs are to be useful in getting at mechanism of action of mental aberrations, a quantitative approach when possible seems essential.

Comment.—The relationship of the predrug personality structure and the type of drug reaction was not as apparent with these drugs as with some others studied, but the correlation of the amount of induced change and the degree of pre-existing maladjustment implies the presence of a significant relationship.[121] This finding suggests McFarland's work[77] on anoxia where he found a high correlation in neurotics between symptom formation, including physical collapse, and low levels of anoxia (induced by simulated high altitudes) where the normal individual was unaffected.

It is important to keep in mind, as von Felsinger, Lasagna, and Beecher[121] point out, that when evaluating drug reactions the primary drug changes can constitute a stressful situation for particular individuals, and they may react with vigorous restitutive activity. The fact that many subjects would respond to perceptual alterations and unusual bodily sensations with anxiety is not strange since experimental studies have demonstrated a similar reaction when external cues to depth or distance are altered or made ambiguous. The complete drug reaction may then be best explained in terms of the individual's defense system or his characteristic reaction to stress or threat in general. The paranoid reactions are a case in point. Thus it might be expected that the poorly adjusted individual would react to drugs with greater diversity and more intensity of behavior than other individuals.

It is easy to appreciate the role of psychologic factors in the "secondary" drug reactions which sometimes supersede the initial, expected one.[121] These reactions are most easily understood as the result of the integrative functions of the personality acting to adjust behavior to an acceptable compromise between internal processes and reality demands or, stated another way, constitute restitutive efforts on the part of a threatened personality organization to preserve its integrity or re-establish its equilibrium. Altering the internal components of this balance may create fear or panic, and great efforts may be made to integrate the change in an emotionally acceptable manner. This may be the best

explanation of religious revelations following ritual drugs and philosophic formulations during the use of mescaline.

The above situation seems analogous to psychologic defense mechanisms developed as a result of threatening disturbances of intrapsychic mechanisms of interpersonal relationships.[121] The defense mechanism of denial is an example in point. It is an interesting, but unexplained, observation in drug experiments in this laboratory that denial appears to be most frequently employed by subjects characterized by a psychopathic personality structure. Another observation of this laboratory is that panic or near-panic as a reaction to drugs seems characteristic of personalities struggling with very strong sexual problems, primarily those of a homosexual nature.[121]

The use of drugs to produce a "psychosis in miniature" and to produce secondary defense reactions in order to study experimentally the relationship of defense pattern and its determinants offers interesting possibilities. An extreme example of drug effect on the development and choice of defense mechanism was the reaction of a young college student (following lysergic acid diethylamide) whose integrative efforts during the drug sessions constituted "the most important experience of my life."[121] The "insight" consisted of a decision that "positive action" was the key to interpersonal relations. When first seen (predrug interview), he was characterized by an excessive desire to please and an anxious ingratiating manner. In the interview he was depressed and anxious over his inability to establish himself in peer groups and showed constant preoccupation with the possibility of acquaintances not liking him. As an example of his difficulties he gave his inability to take any side of an issue under discussion for fear of offending one or the other side. Under lysergic acid diethylamide he was frightened by a feeling of waning contact with reality and doubts of the presence of objects. This was mitigated by self-reassuring statements and positive assertions: "That *is* the chair," "The doctor *is* here," and so on. The effectiveness of this restitutive activity was so anxiety-reducing that the subject suddenly saw it as a key to adjustment and happiness. On return to college he put "positive assertion" into action with friends, girls, classes, and the like, and two months later reported himself to be "successful and happy" in everything he had undertaken. Unfortunately, restitutive activity is rarely so effective.[121]

A basic question is whether drugs create something new in the organism or only release that which is already present. In previous study of other drugs von Felsinger, Lasagna, and Beecher[120] and Lasagna, von Felsinger, and Beecher[68] have been impressed with the apparent meaningfulness of the atypical drug reaction in terms of the individual's personality structure and current personal problems. The small sample and the diversity of response to lysergic acid diethylamide and lysergic acid ethylamide obscure such a relationship if it exists here, but the Rorschach changes are suggestive.

Lysergic acid diethylamide has produced greater and more profound changes in the results of Rorschach testing than any other drug studied in this laboratory.[121] These changes are not striking conversions of normal to psychotic, but rather consistent expansive exaggerations of the predrug personality in which structural weaknesses and immature factors are magnified. In some individuals

already characterized by pathologic signs, such a process may produce a "psychotic" picture. The process itself is better viewed, perhaps, as a release of existing tendencies rather than a creation of new elements.

Quantitative Data.—The writer has no wish to emphasize the need for a quantitative approach to the point of absurdity, where one attempts to quantify the patently unquantifiable. Errors in this direction are likely to be fewer than in the opposite. The pity is, so little has been tried, as Thoreau might have put it. Many are agreed with the need for quantitative data. Gerard[37] says:

> "I am satisfied that the greatest barrier to rapid advance in psychiatric research today is the continuous and anecdotal character of the descriptive material on which psychiatric insights and generalizations are almost exclusively based. When more useful categories have been recognized and at least ordinal scales established; when it is possible to group the phenomena into classes and categories in a meaningful manner, rapid progress is certain to follow. This is really the familiar problem of nosology in disease or typology in individuals or populations. But this implies just the kind of interplay between continuous and discontinuous that has been under discussion. When the input to our biological calculators has been effectively coded, the rules of operation already built into these nervous systems will suffice to grind out important answers in the mental area, as they have already in the physical and biological ones."

A carefully designed experiment carried out in Acheson's laboratory by a large group[38] confirmed the Beecher group's experience[8,9] that introspective data are reliable for scientific investigation in psychopharmacologic relationships.

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Announcement

The ARTHRITIS AND RHEUMATISM FOUNDATION offers predoctoral, postdoctoral, and senior investigatorship awards in the fundamental sciences related to arthritis for work beginning July 1, 1959. Deadline for applications is Oct. 31, 1958.

These awards are intended as fellowships to advance the training of young men and women of promise for an investigative or teaching career. They are not in the nature of a grant-in-aid in support of a research project.

The program provides for three awards:

(1) *Predoctoral Fellowships* are limited to students who hold a bachelor's degree. Each applicant studying for an advanced degree must be acceptable to the individual under whom the work will be done. These Fellowships are tenable for one year, with prospect of renewal. Stipends range from $1,500 to $3,000 per year, depending upon the family responsibilities of the Fellow.

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(3) *Senior Investigator Awards* are made to candidates holding or eligible for a "faculty rank" such as Instructor or Assistant Professor (or equivalent) and who are sponsored by their institution. Stipends are from $6,000 to $7,500 per year and are tenable for five years.

A sum of $500 will be paid to cover the laboratory expenses of each postdoctoral fellow and senior investigator. An equal sum will be paid to cover the tuition expenses of each predoctoral fellow.

For further information and application forms, address the Medical Director, Arthritis and Rheumatism Foundation, 10 Columbus Circle, New York 19, N.Y.

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